ARIC Manuscript Proposal #2075

PC Reviewed: 4/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title:

Incidence and prognostic significance of clinically manifest vs. silent myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):

Silent myocardial infarction

2. Writing Group:
Writing group members:

Zhu-ming Zhang, Pentti Rautaharju, Carlos J. Rodriguez, Laura Loehr, Wayne Rosamond, Dalane Kitzman, David Couper, Elsayed Z Soliman

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]**

First author:

Zhu-Ming Zhang, MD, MPH, FAHA

Address:
Epidemiological Cardiology Research Center (EPICARE)
Wake Forest School of Medicine
Medical Center Blvd. (Wells Fargo-13)
Winston-Salem, NC 27157
Phone: (336)716-0835 Fax: (336) 716-0834
Email: zmzhang@wakehealth.edu

Corresponding author (must be an ARIC investigator for the proposal but can be different in the published paper; correspondence will be sent to both the first author & the corresponding author**)**:

Elsayed Z Soliman,, MD, MSc, MS
Address:
Epidemiological Cardiology Research Center (EPICARE)
Wake Forest School of Medicine
Medical Center Blvd. (Wells Fargo-13)
Winston-Salem, NC 27157
Phone: (336)716-8632 Fax: (336) 716-0834

Email: esoliman@wakehealth.edu

3. Timeline:

Start analyses: upon receipt of data from the coordinating center.
Submission for publication: December 2013.

4. Rationale:

Cardiovascular disease (CVD) is a global health problem. In 2009, CVD was responsible for approximately 790,000 (32.7%) of the 2.44 million deaths in the United States, with coronary heart disease (CHD) alone accounting for about 1 of every 6 deaths. Currently, the estimated annual incidence of myocardial infarction (MI) is 635,000 new attacks, 280,000 recurrent attacks, and an additional 150,000 silent first MI.[1-6]

The 12-lead electrocardiogram (ECG) is a key diagnostic tool for MI and myocardial ischemia, having the advantage of being inexpensive and widely available. The ECG is not only useful when dynamic changes are expected as in patients with acute coronary syndrome, but also in patients with static findings on the routine ECG are a simple way of stratifying patients' risk for CVD mortality.[7-12] Despite the currently available more specific biomarkers of myocardial necrosis, ECG remains an integral part of the diagnostic work-up of patients with suspected MI in clinical settings[4] Further, ECG criteria for MI and ischemia have been used as evidence for CHD in epidemiological studies and clinical trials.[13-15]

Casually discovered asymptomatic MIs with no previous history of MI (i.e. silent MI) are estimated to account for about 21% of all MIs[1]. Differences in incidence and prognostic significance between silent MIs and MIs with clinical manifestations have not been clearly established.

Therefore, the aim of this proposed study is to compare incidence of clinically detected MI and silent MI and to evaluate their value as predictors of subsequent CHD events (fatal and non-fatal) and all-cause mortality.

The ARIC study with its high quality digital ECG data and carefully documented outcome events provides a unique opportunity to address these issues specified above as the goals of this proposal.

5. Main Hypothesis/Study Questions:

This study aims to:

(1) Compare incidence of clinically detected MI (clinical MI) and silent MI (defined as ECG evidence of MI with no history of clinical MI) in the Atherosclerosis Risk in Communities (ARIC) study;

(2) Compare the predictive value of clinical MI and silent MI for subsequent CHD events (fatal and non-fatal), CVD (as stroke, heart failure, peripheral vascular disease), and all-cause mortality;

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).

Sample Size

All ARIC participants with good quality ECG data at both visit 1 and visit 4 as well as information on relevant risk factors and outcome events during study's long term follow-up will be eligible for inclusion in this analysis. Partcipants with MI by ECG or past medical histotry at visit 1 will be excluded.

Variables:

Outcomes:

- All-cause mortality occurring after ARIC visit 4.
- Adjudicated CHD events (fatal and non-fatal) occurring after ARIC visit 4.
- Adjudicated CVD events occurring after ARIC visit 4.

Main exposure variables:

- Clinical MI will be defined as definite or probable adjudicated MI occurring in the period from ARIC visit 1 to ARIC visit 4.

- Silent MI will be defined as ECG evidence of MI based on Minnesota code in the absence of clinically detected in the same period (visit 1 to visit 4).

Other Variables

- All ECG Minnesota codes for MI and other codes at the ARIC visits of 1-4.
- Key demographic and clinical variables -- age, race, gender, body mass index, education, smoking status, alcohol use, hypertension, diabetes mellitus, previous stroke, history of cardiovascular disease, family history of coronary heart disease, HDL cholesterol, LDL cholesterol, total triglycerides, total cholesterol, systolic blood pressure, diastolic blood pressure, baseline fasting blood glucose, urea and creatinine.

Data analysis:

First, frequency distributions of all ECG and non-ECG variables will be inspected to rule out anomalies and outliers possibly due to measurement artifacts.

For aim # 1 (Incidence of silent and clinical MI): During the period from visit 1 to visit 4, incidence rates of silent MI and clinical MI will be calculated per 1000 person years and compared in all ARIC participants as well as stratified by age, sex and race/ethnicity.

For aim # 2 (prognostic significance of silent and clinical MI): For the purpose of this analysis, visit 1 to visit 4 will be considered as the baseline at which silent and clinical MI will be detected. On the other hand, the follow-up period at which outcomes (subsequent CHD events, CVD events, and all-cause mortality) will be evaluated will start after visit 4 until the latest available adjudicated CHD/CVD events. Cox regression analysis will be used to examine the risk of subsequent CHD/CVD events and all-cause mortality (separately) occurring after ARIC visit 4 associated with silent MI and clinical MI (separately).

Models will be initially adjusted for demographic (age, gender, race), then further adjusted for clinical characteristics (which are the variables mentioned as non-ECG variables above). Interaction by sex and race will be examined.

Analytic considerations:

Aim#1: It is important to count the person-years of follow-up the same way for those who have a silent MI and those who have a clinical MI. The exact dates of clinical MIs are known, but the dates of silent MIs are not (will be counted at the visit they are detected). Hence, there is a potential for bias if for clinical MIs we use time until the date of the MI but for silent MIs we use the time until the visit at which the silent MI is detected. Therefore, we will probably need to include the time until participants with clinical MIs would have had their next visit.

Aim #2: It is not necessary to start the time scale for follow up at visit 4. We could start it at the visit at which a silent MI is detected or, for clinical MIs, the first visit after the date of event. However, this floating baseline may complicate the interpretation of the baseline variables included in the models which may negatively impact the readability of the paper. Therefore, we will start follow up time from visit 4, with adding as a covariate how many visits earlier the initial event was detected.

The proportional hazards assumption of the Cox regression model will be checked graphically for each of the candidate variables. All analyses will be performed with the SAS software, version 9.3.

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* _____ **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)?

We are not aware of any.

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.

References:

1- Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. AHA Statistical Update. Heart Disease and stroke statistics – 2013 Update. A report from the American Heart Association. *Circulation* 2013; 127:e6-e245

2- Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined –a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *J Am Coll Cardiol.* 2000;36:959–969.

3- Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies. A statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation.* 2003;108:2543–2549.

4- Thygesen K, Alpert JS, White HD on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal Definition of Myocardial Infarction. *Circulation.* 2007;116:2634-2653

5- Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 2010;362:2155-2165.

6- Kannel WB and Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham Study. *N Engl J Med* 1884;311:1144-1152.

7- 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.

8- Rautaharju PM, Prineas RJ, Wood J, Zhang ZM, Crow R, Heiss G: Electrocardiographic predictors of new-onset heart failure in men and women free of coronary heart disease (from the Atherosclerosis in Communities [ARIC] Study). *Am J Cardiol* 2007;100:1437-1441.

9- Zhang ZM, Prineas RJ, Eaton CB: Evaluation and comparison of the Minnesota code and Novacode for electrocardiographic Q-ST wave abnormalities for the independent prediction of incident coronary heart disease and total mortality (from the Women's Health Initiative). *Am J Cardiol* 2010;106(1):18-25.

10- Zhang ZM, Prineas RJ, Case D, Psaty BM, Suzuki T, Burke GL: Gender Differences between the Minnesota Code and Novacode Electrocardiographic Prognostication of Coronary Heart Disease in the Cardiovascular Health Study *Am J Cardiol* 2011;107(6):817-820

11- Zhang ZM, Prineas RJ, Soliman EZ, Chris Baggett, Gerardo Heiss for the ARIC Research Group: Comparison of the Prognostic Significance of Serial Q/STT Changes by the Minnesota Code and Novacode in the Atherosclerosis Risk in Communities (ARIC) Study. *Eur J Prev Cardiol* 2012;19(6)1430-1436.

12- Zhang ZM, Rautaharju PM, Soliman EZ, Manson JE, Cain ME, Martin LW, Bavry A, Metha L, Vitolins M, Prineas RJ. Mortality Risk Associated with Bundle Branch Blocks and Associated Repolarization Abnormalities: The Women's Health Initiative (WHI). *Am J Cardiol* 2012;110:1489-1495

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

14- Prineas RJ, Crow RS, Zhang ZM. The Minnesota Code Manual of Electrocardiographic Findings (Second edition). Published by Springer-London, 2009.

15- 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