

ARIC Manuscript Proposal # 3186

PC Reviewed: 6/12/18
SC Reviewed: _____

Status: _____
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Priority: 2
Priority: _____

1.a. Full Title: Electrocardiographic Criteria for Silent Myocardial Infarction: Impact of Different Definitions on Detection Rates and Prognostic Significance in the Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:

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

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3. Timeline: Penultimate manuscript submission to the Publications Committee expected within 6-12 months.

4. Rationale:

Over 155,000 asymptomatic silent myocardial infarctions (MIs) are discovered annually in the United States(1). The reported incidence of SMI ranges from 22% to 60% of the total MI incidence, and the prognosis of SMIs is similar or potentially worse than clinically recognized MIs (CMIs) (2). The wide variation in the incidence rates of SMIs results from the differences by which SMIs are defined. Different modalities, such as electrocardiograms (ECG) or cardiac MRI, detect SMIs at different rates, and even studies using the same method yield different rates of SMI.

Most studies evaluating SMIs derive their findings from ECG data. However, different criteria exist to identify SMIs from ECG. In principle, SMI is defined from ECG as presence of pathological Q waves indicating an MI in the absence of evidence of a prior clinical MI. Nevertheless, differences among studies stem from how ECG-evidence of MI as well as prior clinical MI are defined. A self-reported prior history of a clinical MI, which is typically used in cross-sectional studies, is susceptible to recall bias but easy to collect. On the other hand, ascertainment of a prior clinical MI via review of hospital admissions records by an adjudication committee, which is used in longitudinal studies, is more accurate but could be logistically challenging. Each of these methods could yield different estimates for SMI, and subsequently different levels of associations with outcomes.

Similarly, there are several methods to define pathological Q/new MI from ECG, and yet all considered standard approaches (12, 13). ECG-MI could be defined by Minnesota ECG classification, the most commonly used ECG classification in population studies, as presence of a major Q/QS wave abnormality (MC1.1 or MC1.2) or minor Q/QS waves abnormality (MC 1.3) with major ST-T abnormality (MC 4.1, MC4.2, MC5.1 or MC5.2). Utilizing that definition, SMI could be defined as presence of ECG-MI by Minnesota code at one point of time in the absence of prior history of self-reported MI. This approach has been used in cross-sectional studies (3-5). When multiple exam visits are available in longitudinal studies, the same ECG-MI definition also could be used to define new silent MI. In that case, new silent MI in a follow up visit could be defined as presence of evidence of ECG-MI by Minnesota code in that visit without evidence of a prior ECG-MI or clinical MI in a prior visit (6,7). Another more specific approach that also uses Minnesota ECG Classification is called QSTT Serial changes (8). This approach takes into account not only developing new ECG-MI by Minnesota code as previously defined in a follow up visit, but also requires significant changes in the amplitude and/or duration of the QSTT waveforms. Minor modifications to each of these approaches have also been reported. For example, instead of defining new MI from serial changes as codes Q1-Q7, using Q1-Q8 has been used (9,10).

Each approach would expectedly yield different rates for SMI and may have different associations with outcomes. However, these assertions remain un-tested. Furthermore, previous reports showed differences in the incidence and prognostic significance of SMI by sex and race, and hence, it is possible that sex and race modify the relationship between SMI definition with outcomes (6, 7, 11). Therefore, the aims of this study are to examine the impact of the method by which SMI is defined on the observed rates and prognostic significance of SMI, and the race and sex differences in these associations

5. Main Hypothesis/Study Questions:

- 1) To examine the impact of the method by which silent MI is defined on the observed rates of silent MI in the ARIC study, overall and stratified by sex and race
- 2) To compare the associations of silent MI using different definitions with CHD events, CVD events and all-cause mortality
- 3) To examine the impact of sex and race on the relationship between SMI definition with CHD events, CVD events 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 methodologic limitations or challenges if present).

Inclusion/Exclusion Criteria:

We will include ARIC participants with good quality and complete ECG data at ARIC visits 1 through 4 and have follow up data after visit 4. We will exclude participants with prevalent CVD at baseline (visit 1) which includes coronary artery disease (ECG evidence of MI or a self-reported history of physician-diagnosed MI, coronary artery bypass surgery, or coronary angioplasty), history of stroke and history of heart failure. Since we will focus on SMI only, we will also exclude participants with clinical MI after baseline and before visit 4.

Variables:

Silent MI:

In collaboration with the ARIC ECG Reading Center (represented in the proposal), the following definitions of silent MI will be developed based on ECG data and adjudicated clinical MIs between visits 1 and 4:

- 1) Definition #1: SMI will be defined as presence of Minnesota Code ECG-MI [Major Q waves abnormality (MC 1.1 or MC 1.2) or minor Q/QS waves abnormality (MC 1.3) with major ST-T abnormality (MC 4.1, MC 4.2, MC 5.1 or MC 5.2)] in a follow up visit without evidence of a Minnesota Code ECG-MI or clinical MI *by adjudication* in the prior visit during visits 1 to 4.
 - a. In additional analysis, we will consider a definition that only uses major Q waves abnormality (MC 1.1 or MC 1.2); “*Definition #1-a*”
- 2) Definition #2: SMI will be defined as presence of Minnesota Code Serial Changes [codes Q1 to Q7] in a follow up visit without evidence of a clinical MI *by adjudication* in the prior visit during visits 1 to 4.
 - a. In additional analysis, we will consider a definition that only uses Serial Changes codes Q1 to Q8; “*Definition #2-a*”
- 3) Definition #3 (visit 4 only): SMI will be defined as presence of Minnesota Code ECG-MI [Major Q waves abnormality (MC 1.1 or MC 1.2) or minor Q/QS waves abnormality (MC 1.3) with major ST-T abnormality (MC 4.1, MC 4.2, MC 5.1 or MC 5.2)] in *visit 4* without *self-reported* history of a prior MI before visit 4.
 - a. In additional analysis, we will consider a definition that only uses major Q waves abnormality (MC 1.1 or MC 1.2); “*Definition #3-a*”

- 4) Evolving ST-depression/T wave inversion: all ST-T1- ST-T7, in the absence of interim documented clinical MIs
- 5) Evolving bundle branch block: E-BBB1- E-BBB3, in the absence of interim documented clinical MIs

Outcome variables: Fatal and non-fatal CHD events, fatal and non-fatal CVD events, and all-cause mortality occurring after visit 4.

Covariates: Age, gender, race, education level, body mass index, LDL-cholesterol, smoking status, systolic blood pressure, use of blood pressure medications, use of lipid lowering medications, and diabetes mellitus

Statistical Analysis:

Baseline characteristics will be summarized and stratified by MI status (no MI, and SMI). The chi-square test and t-test will be used to compare participant characteristics, as appropriate.

The rates of SMI by different definitions will be calculated, overall and stratified by race and sex and compared using Chi-square/Logistic Regression. Initial analyses will focus on the entire cohort, and secondarily, stratified analyses according to race and sex groups will be employed to further describe significant relationships. Adjustment will be made for baseline demographics (age, race, and sex).

Kaplan-Meier estimates and the log-rank test will be used to compare the cumulative rates of each outcome stratified by MI status and each SMI definition, separately. Participants will be censored at the time of event, death, or at the end of follow-up.

Cox proportional hazards analysis will be used to examine the association between SMI (vs. no MI) with each type of outcome event (CHD events, CVD events, and all-cause mortality), separately occurring after visit 4. We will test the validity of the proportional hazards assumption by visually inspecting the log-log plots. Model 1 will be unadjusted. Model 2 will adjust for demographic characteristics. Model 3 will include covariates from Model 2 plus LDL-cholesterol level, body mass index, smoking status, systolic blood pressure, antihypertensive medication use, and diabetes.

Stratified analysis by race and sex will be conducted in models adjusted in a similar fashion to model 3, and the p values for interaction will be calculated in each subgroup.

The threshold of statistical significance will be set at $\alpha = 0.05$ in all analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes
 __XX__ 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 ICTDER 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 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.csc.unc.edu/ARIC/search.php>

☒ 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)?

- Qureshi WT, Zhang ZM, Chang PP, Rosamond WD, Kitzman DW, Wagenknecht LE, Soliman EZ. Silent Myocardial Infarction and Long-Term Risk of Heart Failure: The ARIC Study. *J Am Coll Cardiol.* 2018;71(1):1-8.
- Zhang Z-M, Rautaharju PM, Prineas RJ, Rodriguez CJ, Loefer L, Rosamond WD, Kitzman D, Couper D, Soliman EZ. Race and sex differences in the incidence and prognostic significance of silent myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 2016;22:2141-2148.

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

☐ 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.csc.unc.edu/aric/forms/>

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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4. Levitan EB, Gamboa C, Safford MM, Rizk DV, Brown TM, Soliman EZ, et al. Cardioprotective medication use and risk factor control among US adults with unrecognized myocardial infarction: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Vasc Health Risk Manag*. 2013;**9**:47-55. PubMed PMID: 23404361. Pubmed Central PMCID: 3569379. Epub 2013/02/14. eng.
5. Levitan EB, Safford MM, Kilgore ML, Soliman EZ, Glasser SP, Judd SE, et al. Assessment tools for unrecognized myocardial infarction: a cross-sectional analysis of the REasons for Geographic and Racial Differences in Stroke population. *BMC Cardiovasc Disord*. 2013 Mar 26;**13**:23. PubMed PMID: 23530553. Pubmed Central PMCID: 3617994. Epub 2013/03/28. eng.
6. Zhang ZM, Rautaharju PM, Prineas RJ, Rodriguez CJ, Loehr L, Rosamond WD, et al. Race and Sex Differences in the Incidence and Prognostic Significance of Silent Myocardial Infarction in the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2016 May 31;**133**(22):2141-8. PubMed PMID: 27185168. Pubmed Central PMCID: 4889519. Epub 2016/05/18. eng.
7. Qureshi WT, Zhang ZM, Chang PP, Rosamond WD, Kitzman DW, Wagenknecht LE, et al. Silent Myocardial Infarction and Long-Term Risk of Heart Failure: The ARIC Study. *Journal of the American College of Cardiology*. 2018 Jan 2;**71**(1):1-8. PubMed PMID: 29301615. Pubmed Central PMCID: 5757248. Epub 2018/01/06. eng.
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13. Prineas RJ, Crow RS, Zhang ZM. The Minnesota Code Manual of Electrocardiographic Findings (Second edition). Published by Springer-London, 2010