1.a. Full Title: Silent Myocardial Infarction and the Risk of Incident Ischemic Stroke

b. Abbreviated Title (Length 20 characters): Unrecognized MI and Stroke

2. Writing Group:

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

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3. **Timeline:**
Analysis to begin after Publication Committee approval.
Submission for publication: Within 6 months of the approval of the proposal.

4. **Rationale:**

Ischemic stroke is a leading cause of disability in the United States with about 690,000 new cases occurring every year.\(^1\) One-fifth of these ischemic strokes are classified as cryptogenic because a specific cause cannot be identified.\(^2\) Identifying new risk factors has the potential to minimize the burden of stroke-related mortality, morbidity, and health care costs.

Clinically apparent myocardial infarction (CMI) is an established independent short-term risk factor for ischemic stroke.\(^3\) Silent MI (SMI), defined as evidence of MI on electrocardiogram (ECG) in the absence of history of CMI, accounts for about one-half of the total number of MIs\(^4-6\) and is associated with an increased risk of heart failure and death.\(^7-9\) However, whether SMI is associated with ischemic stroke similar to CMI is currently uncertain.

CMI causes myocardial scar formation, which leads to abnormal ventricular contraction and, in turn, thrombus formation.\(^10,11\) Ventricular thrombi are associated with a high risk of cardiac embolism and stroke.\(^11-13\) SMI similarly leads to myocardial injury and scar formation.\(^7,14\) Therefore, we propose to examine the hypothesis that SMI is associated with incident ischemic stroke, and specifically that it is more strongly associated with non-lacunar rather than lacunar stroke. The ARIC study provides a valuable opportunity to examine this hypothesis given the availability of digital ECGs, large number of outcome events, and adjudication of stroke subtypes.

5. **Main Hypothesis/Study Questions:**

a) Compared to no MI, SMI is associated with increased risk of incident ischemic stroke.
b) SMI is more strongly associated with incident non-lacunar stroke than with lacunar stroke.

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).**

**Design**

Longitudinal cohort study using prospectively collected data.

**Inclusion/Exclusion Criteria**
We will include all participants with good quality and complete ECG data at ARIC visits 1 through 4. We will exclude participants with prevalent coronary artery disease at baseline (visit 1), defined as the presence of ECG evidence of MI or a self-reported history of physician-
diagnosed MI, coronary artery bypass surgery, coronary angioplasty. In addition, we will exclude participants with prevalent stroke at ARIC visit 1 (baseline).

**Main exposure/predictor variables:**
- SMI: Similar to prior ARIC papers, we will define SMI as ECG evidence of new MI (based on Minnesota codes) at ARIC visit 2, 3, or 4 that was not present at the baseline visit (visit 1) in the absence of documented CMI.
- CMI: CMI will be defined as a new definite or probable adjudicated CMI at ARIC visit 2, 3, or 4 that was not present at the baseline visit (visit 1).

**Outcomes**
- The primary outcome will be incident ischemic stroke, defined as the first occurrence of a hospitalization for ischemic stroke after ARIC baseline visit.
- Secondary outcomes will be incident non-lacunar ischemic stroke and incident lacunar ischemic stroke after ARIC baseline visit.

**Variables**
Other covariates will be ascertained from the baseline (visit 1): age, sex, and race, low density lipoprotein cholesterol level, left ventricular hypertrophy, body mass index, smoking status, systolic blood pressure, antihypertensive and anticoagulant medication use, heart failure, atrial fibrillation, and diabetes.

**Statistical Analyses**
Baseline covariates will be summarized and stratified by MI status (no MI, SMI, and CMI). The chi-square test and ANOVA or t-test will be used for continuous variables. SMI and CMI will be modeled as time-varying covariates. Cumulative incidence rates of stroke per 1,000 person-years will be calculated among participants with no MI, SMI, and CMI. Kaplan-Meier estimates and the log-rank test will be used to compare the cumulative rates of stroke stratified by MI status (no MI, SMI, and CMI). Patients will be censored at the time of ischemic stroke, death, or end of follow up. Cox proportional hazards analysis will be used to examine the association between SMI and CMI (vs. no MI) with stroke. 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 low density lipoprotein cholesterol level, left ventricular hypertrophy by ECG, body mass index, smoking status, systolic blood pressure, antihypertensive and anticoagulant medication use, heart failure, atrial fibrillation, and diabetes. The threshold of statistical significance will be set at $\alpha = 0.05$.

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 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 _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)?


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/

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.cscc.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.
References


