1.a. Full Title: Secular trends in validity of troponin I assays for myocardial infarction classification among four US communities: Findings from the ARIC study

b. Abbreviated Title (Length 26 characters): Trends in troponin ULN

2. Writing Group:
   Writing group members: Matthew Loop, Wayne Rosamond, Aaron Folsom, Jason Fine, Eric Whitsel, Cameron Guild

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___MSL___ [please confirm with your initials electronically or in writing]

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3. Timeline: Exploratory analysis completed. A preliminary analysis for an abstract for AHA EPI | Lifestyle 2018 was submitted in October to the publications committee. A draft of the final analysis will be completed by December 2018.
4. **Rationale:**
The Atherosclerosis Risk In Communities (ARIC) study conducted community surveillance of hospitalized myocardial infarction (MI) from 1987 to 2014 among four US communities (Jackson MS, Forsyth County NC, Washington County MD, and Minneapolis MN). Surveillance of MI during the troponin era (1996 - ) has been complicated by increasing biochemical sensitivity of troponin assays. Although the biochemical sensitivity of such assays has increased, it is unclear to what extent increased assay sensitivity has affected the validity of event classification (e.g., sensitivity and specificity).

The increased sensitivity of troponin assays since their introduction has potentially changed the definition of MI during ARIC surveillance. For example, as evidenced in the final community surveillance report on trends in first MI among the four ARIC communities, crude methods show an increase in the incidence of first MI among blacks from 1987 – 2014. Increased biochemical sensitivity of troponin assays have purportedly led to events being classified as MIs in later years, where the same event would not have been classified as an MI in previous years. Such a trend could indicate decreased specificity of the enzyme diagnosis “abnormal” in ARIC surveillance.

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

We hypothesize that among events that would have been classified by the ARIC computer algorithm as a definite/probable MI or a suspect/no MI regardless of cardiac biomarkers, the sensitivity and specificity of troponin I assays to identify abnormal enzyme levels (ARIC community surveillance criterion: 2x upper limit of normal) has changed over time in hospitals participating in ARIC community surveillance.

1. Has sensitivity/specifictiy of troponin I changed over time?
   a. cases defined as those with evolving diagnostic ECG (will always be a definite MI, regardless of enzymes)
   b. controls defined as those who will always be not an MI regardless of enzymes (no pain and ECG of uncodable or equivocal)

2. Is the change in sensitivity of troponin I assays different between ST-elevation MIs (STEMIs) and non-ST-elevation MIs (NSTEMIs)?

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).**

**Study design:** retrospective, longitudinal analysis

**Inclusion criteria:** All hospitalizations from ARIC community surveillance with a troponin I measurement, which implicitly includes hospitalizations in only years 1996 – 2014 and only in-hospital events (fatal or non-fatal).
Exclusion criteria: ULN for troponin I >= 2 ng/mL; missing stratum variable (NESTVAR_COMBN)

Outcome: When analyzing sensitivity, the outcome will be a 1 if the enzyme diagnosis is “abnormal” and 0 otherwise. When analyzing specificity, the outcome will be a 0 if the enzyme diagnosis is “abnormal” and 0 otherwise. The original enzyme diagnosis (ENZDX) will be used, as opposed to the version that could have been downgraded by a human reviewer.

Other variables of interest

Two key variables of interest are called “always_mi” and “never_mi”. These variables are defined based upon the ARIC computer diagnosis of MI, which uses chest pain, ECG, and enzymes. In some instances, the computer diagnosis will determine an event is a definite or probable MI regardless of cardiac enzymes (i.e., if there is an evolving diagnostic ECG). In other instances, the computer diagnosis will determine an event is a suspect or not an MI regardless of cardiac enzymes (i.e., if there is no chest pain and a normal or missing/uncodable ECG).

Always_MI will have a value of 1 if the computer diagnosis would be a definite or probable MI regardless of cardiac enzymes, and 0 otherwise. Never_mi will have a value of 1 if the computer diagnosis would be a suspect or not an MI regardless of cardiac enzymes, and 0 otherwise. These two variables are used to classify an event as a “case” (for analysis of sensitivity) or a “control” (for analysis of specificity).

Among events classified as cases, we will use an additional classification of whether the event was a STEMI or an NSTEMI.

Data analysis

Descriptive statistics of events will include demographics, year of event, ULN of troponin I assays, troponin I measurements, by whether the event was an “always MI” or a “never MI.” We will also provide estimates of the median ULN of troponin I over time, along with 95% confidence intervals.

Research question 1

We will use two logistic regression models. The first logistic regression model will be restricted to the subpopulation of cases (always_mi = 1), with the appropriate binary outcome variable listed in the “Outcome” section above. The second logistic regression model will be restricted to the subpopulation of controls (never_mi = 1), with the appropriate binary outcome variable listed in “Outcome” section above. Year of the event will be included as a covariate.

From each of the two fitted regression models, we will produce predicted probabilities and 95% confidence intervals for each year, which correspond to estimates of sensitivity and specificity of troponin I assays during each year from 1996 to 2014.
Complex survey procedures that account for the stratified sampling with unequal probabilities among stratum will be used, so that inference can be made on all hospitalizations in the four ARIC communities each year, rather than only the hospitalizations that were abstracted.

It is possible that different hospitals’ propensity to use a given type of assay, with a specific upper limit normal, could vary based upon whether the hospital is a teaching hospital, their tendency to use more current assays (or not), and a myriad of other factors. Our assumption is that the probabilities that hospitalizations could have an abnormal enzyme might be clustered/correlated within specific hospitals. Therefore, as an exploratory analysis we will assess whether including a hospital-specific random effect is warranted by the data.

Research question 2

We will use a logistic regression model restricted to the subpopulation of cases, with the inclusion of an interaction term between year and classification of the event as a STEMI or NSTEMI. The classification of STEMI or NSTEMI will depend on whether there was an ST-segment elevation, as determined by Q waves on the ECG.

We will test for the statistical significance of the group of interaction terms using a Wald test, assuming a type I error rate of 0.1. (Tests for interactions usually have low power, thus the reason for the increased type I error rate above the customary level of 0.05.)

If the interaction is significant, then we will report the predicted probabilities (i.e., sensitivities) for troponin I assays across years separately for STEMI and NSTEMI events.

Methodologic limitations or challenges

The key limitation of this study is the use of always_mi and never_mi variables as a proxy for case and control. In particular, the use of never_mi as identifying controls creates a control group of patients hospitalized for a condition other than MI. Because patients can have elevated troponin I values for reasons other than MI, the specificities obtained in this analysis could be underestimated compared to an analysis using healthy controls. A future ancillary study measuring troponin I values in healthy ARIC cohort participants during a study visit could provide a more reasonable population of controls, and thus provide more generalizable estimates of specificity. However, visits were not conducted in all years from 1996 – 2014.

The exploratory analysis for research question 1 that will include a random effect for hospital will not be entirely straightforward, as there is some debate about how to include random effects in survey-weighted analysis. However, we will explore different options, potentially including Bayesian modeling, in order to perform a robust assessment of whether the probability of having an abnormal troponin I value is clustered within hospital.

The results of our analysis will applicable, however, to a general population of hospitalized patients in four US communities.

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 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)?

#713: Effect of troponin on the assessment of trends in coronary heart disease
#2775: High-sensitivity troponin I and incident heart failure hospitalization, myocardial infarction, stroke and cardiovascular disease mortality in ARIC

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

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.