1. a. Full Title:
Eliminating diagnostic drift in the validation of acute in-hospital myocardial infarction and associated short and long term mortality trends.

b. Abbreviated Title (Length 26 characters): ECG and AMI validation

2. Writing Group:
Writing group members: Richard S. Crow, Peter Hannan, Henry Blackburn, Wayne Rosamond and Aaron Folsom

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

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3. Timeline:
Data analysis completed April, 07. First draft completed September, 07. Manuscript completion June, 08.

4. Rationale:
Long-term trends in epidemiologic studies of AMI require application of a consistent diagnostic algorithm. However, over time significant changes in AMI validation have occurred that challenge the consistency of AMI trends. The use of more sensitive and specific measures of myocardial damage has substantial
implications for in-hospital acute myocardial infarction (AMI) trends and associated short and long term survival after AMI. Given the current, almost universal use of more sensitive biomarkers, troponin, milder and more frequent infarctions are diagnosed now compared to 10 years ago. A diagnosis of MI, driven by more sensitive biomarkers has the potential to create both an artifactual rise in ischemic in-hospital MI event rates and spurious alterations in short and long mortality rates after AMI.

Using Minnesota Heart Survey (MHS) in-hospital cases, we identified 8 ECG criteria (based only on Minnesota Codes) that contributed to a logistic function predicting AMI consistently across years (1970-1995) and consistently for both ICD codes 410/411, and the standard MHS diagnosis. We used multiple cross-validation pairings to validate the robustness of the of the set of eight ECG criteria and found little degradation in the c statistic of the cross-validations.

The ARIC community surveillance monitors admissions to acute care hospitals and death among all residents in four communities. In-hospital MI cases are validated using chest pain, Minnesota Code ECG findings and cardiac enzymes/biomarkers. Identical Minnesota Codes are determined in both MHS and ARIC surveillance from a maximum of 3 ECGs.

We propose to evaluate all age eligible ARIC surveillance cases with discharge codes of 410/411, to apply the logistic prediction function for validation of incident AMI, and to report short and long-term mortality rates in ECG-defined AMI cases.

The electrocardiogram classified by Minnesota Code provides a consistent long-term diagnostic method for determining MI incident rates and severity without the need to adjust for time-varying more sensitive enzymes. These ECG AMI trends and case fatality rates will be compared with the corresponding values using the standard ARIC MI algorithm from 1986-2001 to separate gains from improvement in medical care from improvement in survival by reason of detection of less severe MI’s.

5. Main Hypothesis/Study Question.
We hypothesize that over time the pattern of rates based on a diagnosis of MI at constant severity will differ from the pattern based on “state-of-the-art” ARIC diagnostic algorithm, that likely becomes more sensitive and detects less severe events. Thus, the hypothesis –

Ho: Patterns of MI incidence and survival will differ over time between diagnoses based on the ARIC algorithm versus those based on the ECG logistic score.

Sub-hypothesis: The rates determined by the ARIC algorithm will show increasing incidence and survival rates compared to corresponding rates based on the ECG logistic score.

6. Data (variables, time window, source, inclusions/exclusions):
We will use ARIC Surveillance data, with the Minnesota coded hospital ECG’s, age, gender, ICD codes, enzymes or biomarker used in the standard ARIC MI algorithm, date of hospitalization, follow-up status and length of follow-up.

Analysis plan.
By gender and adjusted or standardized for age, in strata of years such as 1986-1989, 1990-1994, 1995-1999, we will compare the incidence rates and survival rates as determined by two methods - the ARIC MI algorithm or by the ECG logistic score (Crow et al., Am J Epidemiol 161:377-388, 2005). The hypothesis is that the pattern of rates over the year strata determined by the ARIC algorithm detects more MI’s that have improved survival compared to the corresponding rates determined by the ECG logistic score.

Testing for differences in AMI incidence rates between the two methods of diagnosis, involves comparing correlated rates. The denominators are the same, being the population, while the numerators will have some overlap as well as some unique contributions. The delta method for series expansion can be used to approximate the variance of the difference between the two correlated rates. Note that the rates will be positively correlated, so allowing for the correlation will make the test of the difference more sensitive.

Let the incidence rates in an era stratum at time t for those diagnosed MI by the ARIC protocol be \( R_{ARIC} \), and diagnosed by ECG be \( R_{ECG} \).
The variance of the difference in incidence rates will be
\[ \text{Var}(R_{ARIC} - R_{ECG}) = \text{Var}(R_{ARIC}) - 2 \text{Cov}(R_{ARIC}, R_{ECG}) + \text{Var}(R_{ECG}) \]
in which the first and last terms (the variances) can be obtained directly. The complication arises in the covariance. Each method will identify a number of MIs (M_{ARIC} and M_{ECG}) having say M_0 in common, with unique numbers M_{ARIC} and M_{ECG}. We will develop an approximation to \text{Cov}(R_{ARIC}, R_{ECG}) by representing the incidence rates as the ratios \[ R_{ARIC} = (M_0 + M_{ARIC})/N \] and \[ R_{ECG} = (M_0 + M_{ECG})/N \]. The unique parts, represented by the M_{ARIC} and M_{ECG} will be independent, so the covariance will be through the common M_0 and N which will be perfectly correlated across methods.

The same concept, but more complicated implementation, applies for differences in survival (or case-fatality) rates; the extra complication is that the two denominators are correlated, but not the same. The proposed analysis will give us estimated survival probabilities at selected times of follow-up using the ARIC algorithm at time of hospitalization, or correspondingly using the ECG logistic score for diagnosis of MI. We will compare survival curves according to the era of hospitalization, 1986-1989, 1990-1994, 1994-1999 or some such stratification. At any particular follow-up time (eg at 28 days) we will compare the survival rates in an era stratum according to the method of diagnosis. The statistical test of a difference in the survival rates by method of diagnosis must allow for the correlation of the estimated rates. This correlation arises from the overlap of persons diagnosed as MI by both the ARIC protocol and the ECG logistic score.

Let the survival rates in an era stratum at time t for those diagnosed MI by the ARIC be \( S_{ARIC}(t) \), and diagnosed by ECG be \( S_{ECG}(t) \). The variance of the difference in survival rates will be \[ \text{Var}(S_{ARIC}(t) - S_{ECG}(t)) = \text{Var}(S_{ARIC}(t)) - 2 \text{Cov}(S_{ARIC}(t), S_{ECG}(t)) + \text{Var}(S_{ECG}(t)) \]
in which the first and last terms (the variances) can be taken from the output estimating the survival curve. The complication arises in the covariance. At the chosen time t, each method will identify a number of deaths (d_{ARIC} and d_{ECG}) having say d_0 in common, with unique numbers \( \delta_{ARIC} \) and \( \delta_{ECG} \). Similarly each method will identify a risk set \( RS_{ARIC} \) or \( RS_{ECG} \) having \( RS_0 \) members in common with unique extras \( \Delta_{ARIC} \) or \( \Delta_{ECG} \). We will develop an approximation to \( \text{Cov}(S_{ARIC}(t), S_{ECG}(t)) \) by representing the survival rates as the ratios \( S_{ARIC}(t) = (d_0 + \delta_{ARIC})/(RS_0 + \Delta_{ARIC}) \) and \( S_{ECG}(t) = (d_0 + \delta_{ECG})/(RS_0 + \Delta_{ECG}) \). The unique parts, represented by the \( \delta \) and the \( \Delta \) will be independent, so the covariance will be through the common \( d_0 \) and \( RS_0 \) which will be perfectly correlated across methods. Again, the correlation will be positive, so accounting for the correlation will make the comparison test more sensitive.

An alternative method would be to assume the correlation of the \( S_{ARIC}(t) \) with \( S_{ECG}(t) \) is approximately constant over survival times t, and use the sequence of times to calculate a correlation between the two observed series of survival rates. This would be simple but relies on an assumption which may or may not be tenable, or testable.

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 X 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 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 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)?

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.