ARIC Manuscript Proposal # 3046

PC Reviewed: 9/12/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Performance of Shock Index and Modified Shock Index as Predictors of Mortality in Patients Admitted with Acute Myocardial Infarction: The Atherosclerosis Risk in Communities Surveillance Study

b. Abbreviated Title (Length 26 characters): Shock Index: ARIC

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Abstract to be completed for submission to American College of Cardiology (conference deadline 10/10/17). Manuscript to be completed within 1 year of proposal acceptance

4. Rationale:

The Shock Index (SI) is a metric sometimes used in the initial evaluation of a patient to assess hemodynamic status, and has been shown an effective prognostic factor for mortality in trauma patients (Rady et al., 1992). Defined as heart rate divided by systolic blood pressure (HR/SBP), it has proven to be more effective than any vital sign alone at predicting mortality. Multiple studies have examined the various applications of the SI in determining shock and predicting adverse events. One particular area where the SI has been demonstrated as effective is in predicting mortality and/or major adverse cardiac events in patients with an Acute Coronary Syndrome, such as STEMI or NSTEMI (Reinstadler et al., 2016; Kobayashi et al., 2016). These studies showed that in patients requiring PCI for STEMI or NSTEMI, the SI proved an able prognostic factor for developing both short-term and long-term adverse events. Cardiogenic shock has repeatedly been demonstrated as being a strong predictor of in-hospital mortality (Hemradj et al., 2016), but recent studies have suggested that SI is a more sensitive predictor of mortality following PCI for STEMI/NSTEMI (Hemradj et al., 2017).

Although it has been shown that SI is a good predictor of mortality in these patients, it is not a perfect metric and there is a continued search to identify more effective predictors of hospital mortality. A 2015 study examined a new index as a predictor of mortality in this population. Termed the Modified Shock Index (MSI), it is defined as ratio of the heart rate and the mean arterial pressure (HR/MAP). This new metric incorporates the diastolic blood pressure in the index as well, ideally providing a more comprehensive look at the patient's clinical picture. The 2015 study compared MSI to SI in a retrospective study with 160 patients evaluating 7-day outcomes and found that MSI may be more accurate than SI in predicting these events (Shangguan et al., 2017). This study was effective at introducing this new index, however important limitations to this study leave gaps in the research. This study had a relatively low sample size of 160 patients, and the only endpoint examined was a short-term 7-day outcome. It would be useful to understand the long-term prognostic value of the MSI as it compares to the SI. Additionally, this study only evaluated patients with STEMI who received emergency PCI. There are very few studies examining MSI and long-term outcomes as they pertain to patients who present with a variety of acute coronary syndromes.

In this proposed research, we will compare predictive capabilities of SI and MSI in patients with adjudicated classification of acute myocardial infarction (NSTEMI and STEMI), with and without PCI. We aim in this study to evaluate these two indices, SI and MSI, and evaluate all-cause mortality in-hospital, at 28 days, and at one year, something which has not previously been evaluated. Additionally, the large sample size of the ARIC Surveillance Study allows for a high-power evaluation of how these two metrics compare, as well as subgroup analyses within various demographic groups. Determining which metric is the preferred in a given scenario will allow for better prognostication among physicians treating patients with acute coronary events leading to changes in treatment algorithms and overall improvement in patient care.

5. Main Hypothesis/Study Questions:

1. In patients hospitalized with acute myocardial infarction (AMI), is the Modified Shock Index based on the admission heart rate and admission mean arterial blood pressure a better predictor of in-hospital, 28-day, and at 1-year all-cause mortality than the admission systolic blood pressure alone, admission mean arterial blood pressure alone, or the admission Shock Index?
2. Is the Modified Shock Index a better predictor of hospital interventions (such as PCI, CABG, pacemaker, or ICD)?
3. Is shock index or modified shock index predictive of inpatient complications or physician diagnosis of cardiogenic shock?
4. What demographic factors and comorbidities predispose patients to an elevated Shock Index or Modified Shock Index?

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).

Population: Our study population will be limited to patients classified with "definite" or "probable" acute myocardial infarction in the ARIC CHD Community Surveillance Study, sampled from 21 hospitals within 4 US communities from 1987-2014

Exclusion Criteria: Patients without documented vital signs are excluded from this study. Given that this study is examining shock index and modified shock index using the first recorded blood pressure and pulse from the ambulance sheet, ER sheet, clinical graph, or nursing admission note, transfer patients are excluded from this study due to likelihood of prior stabilization. Patients with in-hospital onset of AMI (inferred by chest pain starting after hospitalization) are excluded as this study utilizes vital signs from the ambulance, ER, or at admission. Patients presenting in ventricular fibrillation/cardiac arrest/asystole will be excluded as heart rate will be elevated/unmeasurable and shock index in a patient with these arrhythmias is not a metric with practical prognostic value.

Outcome Variables: Primary outcomes in this study include all-cause mortality in-hospital, at 28 days, and at one year. Secondary outcomes will consist of type of hospital intervention received, including PCI, CABG, ICD, PPM, etc. If available from the hospital record abstractions, physician diagnosis of cardiogenic shock will also be examined as an outcome.

Analytical Plan: Shock Index and Modified Shock Index will be measured both continuously and dichotomously. Previous studies have used 0.7 and 1.4 as cutoff points for SI and MSI, respectively. We will use these but will also conduct our own ROC curve calculations to find ideal cutoff points for these metrics to determine increased or normal SI and MSI. This calculation will be completed by evaluating the Youden's Index and obtaining the J-statistic. The performance of SI, MSI, SBP alone, and MAP alone for prediction of mortality outcomes will be compared using receiver operating characteristics. Subgroup analyses will be carried out in patients with NSTEMI vs. STEMI, those managed invasively vs. medically, women and men, blacks and whites, and older (>65 years) vs. younger patients. All statistical analysis will be performed with the Statistical Analysis System (SAS) software version 9.4, and will be weighted by the inverse of the sampling probability.

Limitations:

- Some patients had no vital signs recorded in the ambulance, ER, or at admission, likely due to severity of clinical presentation or fatality. If possible, a sensitivity analysis with Monte Carlo multiple imputation for missing BP or HR may be considered.
- There is the possibility that patients have been counted in this study more than once. We are unable to address this since patient information has been stripped of all identifying factors.
- Patients transferred to or from other hospitals will be excluded, which could bias the study towards patients who live in urban areas over those living in rural areas.

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)?

There are no proposals to examine shock index or modified shock index in the ARIC study. The most related manuscript proposal is the following:

MS# 617: Evaluation of International Classification of Diseases Codes to Identify Hospitalized Heart Attack Patients with Acute Congestive Heart Failure: The Atherosclerosis Risk in Communities Study

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.

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.