ARIC Manuscript Proposal #

PC Reviewed: ___/___/16 **Status: _____** **Priority: ____**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Fifteen year trends and outcomes of early vs. late NSTEMI revascularization

b. Abbreviated Title (Length 26 characters): Early vs. Late Revascularization in NSTEMI

2. Writing Group:
Sameer Arora, Brandon Stacey, Kunihiro Matsushita, Melissa Caughey, *others welcome and expected*

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: An initial analysis will be prepared for the Society for Cardiovascular Angiography and Interventions (SCAI) conference, which has a March 8th abstract deadline for Late-Breaking science. Following that, a more extensive analysis and manuscript will be drafted. We anticipate completing this project within 1 year of the proposal approval.

4. Rationale:

Previous research has demonstrated the efficacy of invasive procedures for the management of patients with non-ST elevation myocardial infarction (NSTEMI).[1] Reductions in NSTEMI mortality over the years have largely been attributed to standardization and improvement in revascularization techniques.[2] However, the optimal timing for NSTEMI revascularization remains uncertain, as studies continue to show conflicting evidence.[3,4] Currently, the 2014 ACC/AHA guidelines for NSTEMI management recommend early revascularization for initially stabilized patients with high risk of clinical events (Class I, Level of Evidence B).[5] Patients with high risk of clinical events may be identified by various risk scores (TIMI score, Grace scale, Killip class), which incorporate data from the clinical history, physical exam, ECG, renal function, and troponin labs[5]. Aside from patients identified with high risk, the guidelines offer no suggestions for optimal NSTEMI revascularization time.
The ARIC Community Surveillance Study is well suited for the analysis of NSTEMI revascularization trends and outcomes, as well as the impact of early (<24 hours after event onset) vs. late revascularization on mortality outcomes.

5. Main Hypothesis/Study Questions:

Revascularization vs. No Revascularization

1. What are the clinical and demographic predictors of NSTEMI revascularizations? Potential predictors may be age, race, sex, geographic location, insurance status, year of hospitalization, laboratory values, and comorbid conditions.
2. How have annual trends in NSTEMI revascularizations changed from 1987 to 2013? In particular, do annual trends in NSTEMI angiography utilization and revascularization differ by race? Do annual trends in angiography utilization and revascularization differ by race for patients classified with STEMI?
3. What is the impact of revascularization (angioplasty, atherectomy, CABG, thrombolysis) on in-hospital, 30-day, and 1-year mortality in patients hospitalized with definite/probable NSTEMI?

Early vs. Late Revascularization Time

4. What are the clinical and demographic predictors of early and late revascularizations? Potential predictors may be age, race, sex, geographic location, insurance status, year of hospitalization, laboratory values, comorbid conditions, weekday vs. weekend admission, and presentation time to the hospital after event onset.
5. Has the proportion of patients receiving early revascularization (<24 hours after event onset) changed from 2000 to 2015?
6. Among the subset of NSTEMI patients undergoing revascularization, is early (<24 hours after event onset) vs. late (>24 hours) revascularization associated with fewer in-hospital, 30-day, and 1-year deaths?
7. If so, do associations between mortality outcomes and early vs. late revascularization remain significant, after adjusting for time from event onset to hospital admission?

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).

This analysis will be based on hospitalized patients sampled by the ARIC Community Surveillance during the "troponin era" (2000-2015). Our study population will be limited to patients classified with definite or probable NSTEMI. Statistical analyses will be weighted by the inverse of the sampling probability.

Aim 1

-Associations between revascularization and in-hospital, 30-day, and 1-year mortality will be analyzed using Cox regression. Multiple models will be constructed, with adjustment for potential confounders and assessment of statistical interaction.
-Clinical and demographic predictors of revascularization will be modeled by logistic regression with backward elimination.
-Revascularizations by calendar year will be plotted visually. If plots are monotonic and linear, annual trends in revascularization will be assessed by Pearson correlation.

Aim 2

-Among the subset of patients undergoing revascularization, hazard ratios of in-hospital, 30-day, and 1-year mortality will be analyzed, using Cox regression with early revascularization (<24 hours) contrasted with late revascularization. Multiple models will be constructed, with adjustment for potential confounders and assessment of statistical interaction.
-Clinical and demographic predictors of early revascularization will be modeled by logistic regression with backward elimination.
- The proportion of patients receiving early revascularization by calendar year will be plotted visually. If plots are monotonic and linear, annual trends in revascularization will be assessed by Pearson correlation.

Sensitivity Analysis

We will also consider the effect of early vs. late revascularization in a propensity matched analysis. Propensity scores will be derived by a predictive model for early revascularization, based on the subset of patients undergoing revascularization. Patients with and without early revascularization will be matched by their propensity scores for this analysis.

Limitations and challenges:

-Although the exact timing of hospital admission was recorded in the dataset, the exact timing of reperfusion/revascularization does not appear to be. For this reason, we will most likely rely on the yes/no variable for reperfusion <24 hours (HRAA26A). We could use the estimated time from event onset to reperfusion (HRAA26B), but these categories only go up to 8 hours, and many NSTEMI patients presented to the hospital later than 8 hours after event onset.

-A strong potential confounder of the early revascularization benefit may be presentation time to the hospital after event onset. In other words, early revascularization may simply be a function of early presentation to the hospital. The analysis of early vs. late revascularization could also be impacted by selective survival, because patients presenting late to the hospital would necessarily have survived up until that point, and may have a less severe case than those presenting earlier to the hospital. Finally, treatment effects in observational studies are susceptible to confounding by indication, and patients with more severe cases may need to be intervened upon sooner. However, identification of high risk patients by the TIMI score, Grace scale, or Killip class may be difficult, because the inputs for these risk scores are limited by availability in the medical record and the abstraction priority.

-To overcome these challenges, we will adjust for time to presentation, as well as comorbid conditions and hospital values (laboratories, blood pressure, etc) which may suggest more severe cases. We will also conduct a propensity matched analysis of patients undergoing early vs. late presentation. However, an important limitation of the propensity matched analysis is that there is really no valid way to include the sampling weights in the propensity score weights.

7.a. Will the data be used for non-CVD analysis in this manuscript? _x___ 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)?

MP085: Differences in outcomes for myocardial infarction in relation to differences in hospital medical care.
MP971: Use of invasive and noninvasive cardiac diagnostic procedures for hospitalized myocardial infarction; disparities, trends, and outcomes. The Atherosclerosis Risk in Communities Study
MP983: Impact of Insurance Status and Types on Inequities in Hospital Care of Acute Coronary Syndrome
MP1103: Socioeconomic Characteristics and Variation in Rates and Temporal Trends in the Use of Invasive Coronary Procedures in ARIC Community Surveillance
MP2714: Prehospital delay trends and association with survival in ARIC community surveillance.

With the exception of MP2714, all previous proposals are at least 10 years old. Importantly, none of these proposals is related to trends and outcomes of NSTEMI revascularization time.
We contacted Wayne Rosamond (an author on most of these proposals, including MP2714), but have not yet heard back.

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 __x__ No.

Bibliography

1. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E and Investigators TTiMI. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879-87.
2. Movahed MR, John J, Hashemzadeh M and Hashemzadeh M. Mortality trends for non-ST-segment elevation myocardial infarction (NSTEMI) in the United States from 1988 to 2004. *Clin Cardiol*. 2011;34:689-92.
3. Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, Schmitt C, Seyfarth M, Dirschinger J and Schomig A. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290:1593-9.
4. van 't Hof AW, de Vries ST, Dambrink JH, Miedema K, Suryapranata H, Hoorntje JC, Gosselink AT, Zijlstra F and de Boer MJ. A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study. 2b/3a upstream therapy and acute coronary syndromes. *Eur Heart J*. 2003;24:1401-5.
5. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2354-94.