PC Reviewed: 1/9/18   **Status: _____**   **Priority: 2**

SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: 28-year Trends in the Incidence and Management of Acute Myocardial Infarction in the Young Adult Population (1987-2014)

  b. Abbreviated Title (Length 26 characters): MI in Young Adults

2.   Writing Group:

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

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3.   Timeline: The goal is to prepare the manuscript within 1 year of approval of proposal

4. Rationale:

Contemporary analyses of the clinical characteristics, management, and outcomes of young patients with acute myocardial infarction (AMI) are sparse. The incomplete understanding of the epidemiology of AMI in young populations is surprising, considering that this is the group where the largest impact can be made with respect to life expectancy. Although limited to few studies, previous research suggests management and outcomes of young patients with AMI may differ by sex and race. Whether differences exist in AMI management and outcomes for young compared to older patients is unknown. Despite an overall decrease in the annual incidence of AMI (1), reductions in the rate of AMI have not extended to young adults (2,3).

The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO), a prospective cohort study of women and men aged ⩽55 years hospitalized for AMI evaluated sex differences in demographics, healthcare access, cardiovascular risk, and hospital management for AMI (2). Young women with AMI had greater cardiovascular risk factors and comorbidities than young men, including diabetes, congestive heart failure, chronic obstructive pulmonary disease, renal failure, and morbid obesity. Young women were also less likely to undergo revascularization procedures during hospitalization, and those with ST segment elevation myocardial infarction were less likely to receive timely primary reperfusion (2). An analysis from the National Inpatient Sample reported no overall decline in AMI hospitalization rates from 2001 – 2010 for women and men <55 years. However, consistently higher hospitalization rates were noted for young black women compared to young white women from 2001 - 2010. Furthermore, increasing frequencies of comorbidities were observed for both sexes of patients hospitalized with AMI (3). Although in-hospital mortality rates declined for young women over the study period, they continued to exceed men.

Recent interest in younger patients experiencing AMI has motivated formation of the Young MI Registry (4). A recent analysis reported a drastically low proportion (12.5%) of young adult patients on statins at the time of MI (5), which may reflect decreased recognition of CVD risk factors in younger patients prior to MI. This was also demonstrated in the VIRGO study where despite having significant cardiac risk factors, only one-half of young AMI patients believed they were at risk for heart disease before their event (6). Reports of potential disparities in clinical management of young vs. older patients hospitalized with MI are sparse. We propose to leverage data from the ARIC surveillance of coronary heart disease to examine the incidence of MI over time, and describe trends in invasive and medical management of young and older MI patients over time. The ARIC surveillance study has been collecting data on patients with AMI between 35-75 years of age during the entire years of the study and 35-85 years of age from 2005 onwards and therefore, provides a perfect platform to evaluate the trends in incidence, clinical characteristics and management of these patients. Additionally, the stratified sampling design of the ARIC surveillance study will allow a comprehensive analysis of trends stratified by sex and by race.

5.   Main Hypothesis/Study Question

1. What are the clinical and demographic characteristics of young patients hospitalized with STEMI and NSTEMI from 1987 to 2014? Variables of interest may include race, sex, geographic location, insurance status, laboratory values, and comorbid conditions. How do they compare to older patients (55-75 years) with STEMI and NSTEMI?
2. What are the trends in incidence of MI in the young adult population (35 - 54 years of age), stratified by race, sex, and type of MI (STEMI and NSTEMI)? How do these trends compare to trends in the incidence of MI in the older population (55 – 75 years)?
3. What are the trends in mortality (in-hospital, 28-day, and 1-year) of the young adult NSTEMI and STEMI population, stratified by age and sex? How has mortality changed over time? How does mortality compare to that of older patients (55 – 75 years)
4. What are the trends in management (angiography, revascularization [PCI or CABG], echo, stress test, medications [aspirin, antiplatelets, beta blockers, ACEi, and lipid lowering agents]) of patients with NSTEMI and STEMI in young adult population, stratified by age and sex? How have they changed over time? How do they compare to older patients?
5. What are the trends in risk factors of young patients with STEMI and NSTEMI? Variables of interest are smoking, diabetes mellitus, hypertension, chronic kidney disease/end stage renal disease, previous PCI or CABG/CAD. How do they compare to older patients (55-75 years) with STEMI and NSTEMI?

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).

<u>**Analytical Plan**</u>

-All statistical analyses will be carried out using SAS Survey Procedures, and will be weighted by the inverse of the sampling probability (SAMWT_TRIM variable), accounting for the stratified sampling design (NESTVAR variable).

-Patients with incident MI will be stratified into young (<55 years) vs. older (55-75 years) age categories. Categorical variables will be compared using Rao-Scott χ^2 tests. Continuous variables will be compared using the difference in least squares means from weighted linear regression.

-Annual trends in the proportion of patients experiencing outcomes of interest will be plotted and visually assessed. If linear and monotonic, trends over time will be analyzed using the Pearson correlation trend test.

-Multivariable logistic regression models will be used to compare in-hospital mortality and clinical management outcomes among young and older patients. Multivariable Cox regression will be used to analyse longer term outcomes (28-day and 1-year mortality). Models will be adjusted for potential confounders. Effect modification by sex and race will be analysed by multiplicative interaction. Trends in annual risk ratios over time will be analysed by Pearson correlation trend test.

-In a sensitivity analysis, the effectiveness of revascularization [PCI / CABG] on mortality outcomes [28-day, 1-year] will be assessed in propensity-matched analyses. Separate PS matched-pair populations will be created for young patients with STEMI, young patients with NSTEMI, older patients with STEMI, and older patients with NSTEMI. Propensity scores reflecting the probability that patients receive revascularization therapy will be derived, using demographic information and available comorbidities abstracted from the medical record, or possibly ICD codes. The appropriateness of PS-matched analyses will be assessed by ascertaining covariate balance among the matched pairs. For each of the 4 matched-pair populations (young NSTEMI, young STEMI, older NSTEMI, older STEMI), the absolute risk reduction in 28-day and 1-year mortality associated with revascularization will be analysed.

Limitations and challenges:

-Data are limited to availability in the medical record and the abstraction priority. Many procedures and medications weren't abstracted from the medical record until the late 1990s. Thus, we will examine trends in CVD risk factors and incidence of NSTEMI / STEMI from 1987-2015, trends in revascularization (PCI or CABG) from 1987-2015, and trends in stress testing, echocardiography, and medications from 2000 onward.

-Odds ratios will overestimate relative risk for common outcomes. Because outcomes such as aspirin, beta blocker, antiplatelet, and statin use are expected to be common, the odds ratios will be converted to risk ratios.

-We will not know which type of "non-aspirin antiplatelet" was administered, nor will we know if "lipid lowering medication" denotes statins, or some other medication such as fibrates or niacin.

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

MP999: Differences in Case Fatality Rates Following ST-elevation MI, Non-ST-elevation MI, and Unstable Angina, 1987-2000

MP2153: Trends in incidence of hospitalized STEMI and NSTEMI and CHD mortality among 35-84 year olds in ARIC Community Surveillance 2005-2014

MP2336: Trends in Atypical Presentation of Myocardial Infarction: Atherosclerosis Risk in Communities (ARIC) Surveillance, 1987-2010

The first 4 proposals are at least 10 years old. Importantly, none of these proposals is related to AMI in young populations.

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. Eisen A, Giugliano RP, Braunwald E. Updates on Acute Coronary Syndrome: A Review. JAMA Cardiol 2016;1:718-30.

2. Gupta A, Wang Y, Spertus JA et al. Trends in acute myocardial infarction in young patients and differences by sex and race, 2001 to 2010. J Am Coll Cardiol 2014;64:337- 45.

3. Bucholz EM, Strait KM, Dreyer RP et al. Sex differences in young patients with acute myocardial infarction: A VIRGO study analysis. Eur Heart J Acute Cardiovasc Care 2017.

4. Singh A, Collins B, Qamar A, Gupta A, Fatima A, Divakaran S, Klein J, Hainer J, Jarolim P, Shah RV, Nasir K, Di Carli MF, Bhatt DL and Blankstein R. Study of young patients with myocardial infarction: Design and rationale of the YOUNG-MI Registry. *Clin Cardiol*. 2017;40:955-961.

5.Singh A, Collins BL, Gupta A, Fatima A, Qamar A, Biery D, Baez J, Cawley M, Klein J, Hainer J, Plutzky J, Cannon CP, Nasir K, Di Carli MF, Bhatt DL and Blankstein R. Cardiovascular Risk and Statin Eligibility of Young Adults After an Myocardial Infarction: Partners YOUNG-MI Registry. *J Am Coll Cardiol*. 2017.

6.   Leifheit-Limson EC, D'Onofrio G, Daneshvar M, Geda M, Bueno H, Spertus JA, Krumholz HM and Lichtman JH. Sex Differences in Cardiac Risk Factors, Perceived Risk, and Health Care Provider Discussion of Risk and Risk Modification Among Young Patients With Acute Myocardial Infarction: The VIRGO Study. *J Am Coll Cardiol*. 2015;66:1949-1957.