ARIC Manuscript Proposal #3852

PC Reviewed: 6/8/21	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Outcomes in Patients with Myocardial Infarction with Versus Without Standard Modifiable Cardiovascular Risk Factors: Insights from the ARIC study community surveillance.

b. Abbreviated Title (Length 26 characters): **Outcomes of MI with vs without risk factors: ARIC Study**

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

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3. Timeline: Manuscript to be completed within 6 months of proposal approval.

4. Rationale:

In coronary artery disease, targeted strategies against the well-recognized modifiable risk factors of diabetes, hypercholesterolemia, hypertension, and smoking (known as the standard modifiable cardiovascular risk factors [SMuRFs]) have led to major improvements in prevention and treatment[1, 2]. However, a clinically significant proportion of patients present with life threatening myocardial infarction with no previous symptoms, and none of the SMuRFs at or greater than diagnostic thresholds[3].

Patients without SMuRFs are often overlooked in clinical trial publications, which classically report the proportion of patients with known risk factors, but not the proportion with none. On a review of the international guidelines and their referenced trials, there has been an absence of data on the proportion of patients without SMuRFs. Moreover, characteristics and outcomes in this group, including adherence and specific response to secondary prevention therapies, are not known.

A retrospective study showed that the proportion of patients with ST-elevation myocardial infarction (STEMI) without SMuRF increased, from five (10·9%) of 46 patients in 2006, to 26 (27·4%) of 95 patients by 2014[4]. An increase in this population presenting with STEMI without SMuRF was also observed in a large Australian national registry, increasing from 45 (14%) of 337 patients to 132 (23%) of 570 patients between 1999 and 2017.[5] This group had a higher in-hospital mortality rate as compared with patients with at least one SMuRF[5], similar to previous reports in Canadian and US cohorts.[6, 7].This unexpected observation requires further appraisal.

In this study, we will analyze data from patients with first presentation with MI to examine the clinical characteristics of patients without SMuRFs and compare short-term and long-term outcomes with their counterparts with at least one modifiable risk factor. To investigate this, we will examine the community surveillance data captured by ARIC from 1987-2014.

5. Main Hypothesis/Study Questions:

1. What is the prevalence of MI in patients without SMuRF among the total patients hospitalized with MI? Does the prevalence differ within demographic subgroups? Does the prevalence differ based on the type of MI (STEMI vs NSTEMI)?

2. Do clinical characteristics of patients admitted with MI differ between patients with and without SMuRFs?

3. Do the laboratory findings, echocardiographic features and clinical management differ in patients presenting with MI with and without SMuRF?

4. Do the incidence rates of 30-day mortality and MACE differ between MI patients with and without SMuRF? Do these outcomes differ based on the type of MI?

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 Population:
Patients hospitalized with CAD events captured by the ARIC community surveillance between 1987-2014.

Exposure:
Patients with MI, stratified by presence of SMuRFs. Presence of MI was abstracted from the medical record and confirmed with ICD-9 discharge codes.

Outcomes:
- Clinical characteristics and laboratory findings in patients admitted with MI stratified by presence of SMuRFs, as defined in Tables 1-3 below
- Short-term and long-term clinical outcomes in MI patients stratified by presence of SMuRFs, including All-cause mortality, Cardiovascular mortality, recurrent myocardial infarction, heart failure, stroke, revascularization, major bleeding, MACE
    - Death within 30-days and 1-year of the index hospitalization discharge date.
    - Cardiovascular death defined by death due to "diseases of the circulatory system" would be based on ICD-9 codes 390–459 and ICD-10 codes I00-I99.

Exclusion Criteria
We will exclude patients 75–85 years of age as this age group was only sampled between years 2005 to 2014.

Electrocardiography
The first, third, and the last 12-lead electrocardiograms (ECG) over the course of hospitalization will be obtained from the medical record which is coded electronically at the Minneapolis ECG Reading Center.

Chest Pain
Presence of chest pain will be abstracted from the medical record, with origin determined by review of physician notes. Any mention of substernal pressure, tightness, or pain precipitated by exertion or excitement was considered evidence of chest pain of cardiac origin.

Acute Myocardial Infarction Classification
Events classified by the ARIC study as definite, probable, suspected, or no MI, based on ECG evidence (evolving diagnostic, diagnostic, evolving ST-segment/T-wave changes, equivocal, or absent/uncodable), presence of chest pain, and cardiac biomarkers (which were considered "abnormal" if ≥2x the upper limit of normal (ULN), and "equivocal" if exceeding the ULN but <2x the ULN). Classification of an event as definite or probable AMI will be based on the presence of at least one of the following: 1) evolving diagnostic ECG pattern 2) diagnostic ECG pattern and abnormal biomarkers, 3) cardiac pain and abnormal biomarkers, 4) cardiac pain and equivocal biomarkers with evolving ST-segment/T-wave pattern or diagnostic ECG pattern, or 5) abnormal biomarkers with evolving ST-segment/T-wave pattern.

Biomarkers

Laboratory values for biomarkers of cardiac injury will be obtained from values that were recorded for the first 4 days of hospitalization.

Medical Therapies

Medications record based on administration either during hospitalization or prescribed at hospital discharge. Aspirin will require routine rather than *pro re nata* administration for abstraction. Non-aspirin antiplatelet therapy will be recorded as a single category and included $P2Y_{12}$ inhibitors (cangrelor, clopidogrel, prasugrel, ticagrelor, ticlopidine), glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), phosphodiesterase 3 inhibitors (cilostazol), phosphodiesterase 5 inhibitors (dipyridamole), and protease-activated receptor-1 antagonists (vorapaxar). Beta blockers included β_1 adrenergic antagonists. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ACEi/ARB) will be recorded as a single category. Lipid-lowering agents included statins, niacin, and fibrates.

Procedures

Echocardiography, stress testing, angiography and revascularization procedures will be abstracted from the medical record. Echocardiography includes transthoracic and transesophageal echocardiograms. Stress testing included exercise testing (treadmill or bicycle ergometer), stress echocardiography, cardiac stress magnetic resonance imaging, and nuclear stress tests. Revascularization will include percutaneous coronary intervention or coronary artery bypass graft surgery.

Analytical Plan

Continuous variables will be assessed for normality and compared using the difference in least square means from weighted linear regression. Categorical variables will be compared using Wald χ^2 tests. The annual incidence of AMI hospitalizations among patients with and without SMuRFs will be calculated by dividing the weighted number of sampled AMI hospitalizations by the total number of ARIC residents. Similarly, the proportion of AMI hospitalizations that occur in patients with SMuRFs as well as those without will be examined across all years of observation. Trends over time will be described in 5-year intervals (1995–1999, 2000–2004, 2005–2009, 2010–2014) and analyzed using Poisson regression over years. Trends in the prevalence of cardiovascular risk factors in patients with SMuRFs will be also be plotted. Among patients with MI, the relative probabilities of patients with SMuRFs vs those without receiving guideline-directed AMI medications (aspirin, other antiplatelets, beta blockers, and lipid-lowering medications) or undergoing invasive procedures (angiography and revascularization) will be compared in 5-year intervals and in the aggregate. Associations will be derived from multivariable logistic regression, with odds ratios and 95% confidence intervals (CI). Models will be adjusted for race, geographic region, and year of admission. One-year all-cause mortality will be compared between patients with at least one SMuRF and those without using multivariable Cox regression, adjusted for race, geographic location, and year of admission. We will perform several sensitivity analyses. First, we will also stratify our multivariable logistic regression and Cox regression models by race. Second, we will additionally adjust these models for other comorbidities and complications (diabetes mellitus, acute heart failure / pulmonary edema, ventricular fibrillation, cardiac arrest, and cardiogenic

shock). Statistical tests and models will be weighted by the inverse of the sampling probability. All statistical analyses will be carried out using SAS 9.4 (SAS Institute; Cary, NC).

Tables and Figures

Table 1: **Baseline clinical and demographic characteristics of patients with and without SMuRFs in patients with myocardial infarction.**

	Overall	SMuRF-less	≥1 SMuRF
Admission characteristics			
Age			
Sex			
Male			
Female			
Race			
Black			
White			
SMuRF			
DM			
HTN			
Hypercholesterolemia			
Smoking			
BMI			
Smoking Status			
Never/Former smoker			
Current smoker			
Medical history			
Stroke			
Peripheral arterial disease			
Atrial fibrillation			
Heart failure Hospitalization			
Prior revascularization			
Prior myocardial infarction			
COPD			
Chronic Kidney disease			
Cancer			
Prehospital pharmacotherapy			
Statin			
Aspirin			
$P2Y_{12}$ inhibitor			
β-blocker			

ACEIs or ARBs			
Laboratory variables			
Creatinine			
Total cholesterol			
Triglycerides			
HDL cholesterol			
LDL cholesterol			
HbA1C			
Glucose			
CRP			

Table 2: **Presentation characteristics and in-hospital outcomes and management patterns in patients with MI stratified by SMuRF.**

	Overall	**SMuRF-less**	**≥1 SMuRF**
Systolic blood pressure			
Diastolic blood pressure			
Heart rate			
Cardiac arrest at presentation			
Multivessel coronary artery disease			
Troponin T			
Troponin I			
Left ventricular function grade			
EF ≥50%			
EF 40-49%			
EF 30-39%			
EF <30%			
STEMI location			
Anterior			
Inferior			
Lateral			
Multiple			
In-hospital management			
Thrombolysis			
PCI within 24 hours			
CABG within 24 hours			
In-hospital complications			
All-cause death			
In-hospital MACE			

myocardial infarction			
Acute heart failure			
Pulmonary edema			
stroke			
Major bleeding			
Cardiogenic shock			
Ventricular fibrillation/cardiac arrest			
Length of stay, days, median			
Discharge medications			
Statin			
Aspirin			
P2Y12 inhibitor			
β-blocker			
ACEIs or ARBs			

Table 3: **Prevalence and temporal trends in cardiovascular risk factors among patients with SMuRFs presenting with acute myocardial infarction from 1995-2014.**

	1995-1999	2000-2004	2005-2009	2010-2014	Trend *P* value
SMuRFs					
Smoking					
Hypertension					
DM					
Hypercholesterolemia					
Prior MI					

Table 4: **Relative probabilities of guideline-directed therapies, comparing patients with and without SMuRFs presenting with MI.**

SMuRFs vs SMuRF-less relative probability

	1995-1999	2000-2004	2005-2009	2010-2014	Trend *P* value
Aspirin					
Non aspirin antiplatelet					
Lipid lowering agent					
Beta blocker					
Invasive angiography					

Coronary Revascularization					

Figure 1: **Temporal trends in the incidence of MI in patients with and without SMuRFs among residents of the ARIC communities from 1995-2014.**

Figure 2: **Temporal trends in incidence of MI based on ≥1, 2 or 3 SMuRFs.**

Figure 3: **Prevalence and temporal trends in cardiovascular risk factors among patients with and without SMuRFs presenting with MI from 1995-2014.**

Figure 4: **Annual trends in administration of guideline-directed therapies in patients with and without SMuRFs presenting with MI from 1995-2014.**

Figure 5: **Relative probabilities of patients with and without SMuRFs receiving guideline-directed therapies for MI from 1995-2014.**

Figure 6: Forest plot depicting hazard ratios for primary and secondary outcomes between patients with and without SMuRFs (both 30 days and I year outcomes):

1. All-cause mortality
2. Cardiovascular mortality
3. Recurrent myocardial infarction
4. Heart failure
5. Stroke
6. Revascularization
7. Major bleeding
8. MACE

Figure 7: **Kaplan Meier survival curve for all-cause mortality and cardiovascular mortality between patients with and without SMuRFs.**

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)?

None

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.

References

1. Dawber, T.R., F.E. Moore, and G.V. Mann, *Coronary heart disease in the Framingham study.* Am J Public Health Nations Health, 1957. **47**(4 Pt 2): p. 4-24.
2. Piironen, M., et al., *Trends in long-term prognosis after acute coronary syndrome.* Eur J Prev Cardiol, 2017. **24**(3): p. 274-280.
3. Piepoli, M.F., et al., *2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR).* Eur Heart J, 2016. **37**(29): p. 2315-2381.
4. Vernon, S.T., et al., *Increasing proportion of ST elevation myocardial infarction patients with coronary atherosclerosis poorly explained by standard modifiable risk factors.* Eur J Prev Cardiol, 2017. **24**(17): p. 1824-1830.
5. Vernon, S.T., et al., *ST-Segment-Elevation Myocardial Infarction (STEMI) Patients Without Standard Modifiable Cardiovascular Risk Factors-How Common Are They, and What Are Their Outcomes?* J Am Heart Assoc, 2019. **8**(21): p. e013296.
6. Wang, J.Y., et al., *Cardiovascular Risk Factors and In-hospital Mortality in Acute Coronary Syndromes: Insights From the Canadian Global Registry of Acute Coronary Events.* Can J Cardiol, 2015. **31**(12): p. 1455-61.
7. Canto, J.G., et al., *Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction.* Jama, 2011. **306**(19): p. 2120-7.