ARIC Manuscript Proposal #3908

PC Reviewed: 8/10/21	**Status: _____**	**Priority: w**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title: Presentation, Management, and Outcomes of Patients with vs without Diabetes Mellitus who are Hospitalized with Acute Myocardial Infarction: Insights from the ARIC Study Community Surveillance.

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

2. Writing Group: Vardhmaan Jain*, Arman Qamar*, Muthiah Vaduganathan, Deepak L. Bhatt, 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. _VJ **[please confirm with your initials electronically or in writing]**

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3. Timeline: Manuscript to be completed within 4 months of proposal approval.

4. Rationale:

Over 34 million people in the U.S. (~10% of the U.S. population) are reported to have diabetes mellitus (DM).[1] Despite significant therapeutic advancements in the management of diabetes and its associated complications, acute myocardial infarction continues to be a major cause of morbidity and mortality in diabetic patients. In fact, prior studies have shown that diabetes mellitus is independently associated with a 2-4-fold increased risk of cardiovascular events and a 3-fold increased risk of cardiovascular mortality.[2,3] Factors unique to diabetes increase atherosclerotic plaque formation and thrombosis, predisposing patients to myocardial infarction. Autonomic neuropathy may result in atypical presenting symptoms in the diabetic patient, making diagnosis difficult and delaying treatment with evidence-based practice. The clinical course of myocardial infarction is frequently complicated and carries a higher mortality rate in patients with coexisting DM.[4] A large proportion of this increased mortality is attributable to the clustering of traditional risk factors such as obesity, hypertension, and dyslipidemia in patients with DM,[5] as well as unique manifestations of DM such as multi-vessel coronary artery disease and diffuse lesions.

Previous reports from the 2004-2014 Nationwide Inpatient Database suggest worsening acuity of patients hospitalized with AMI in recent years, and a steadily increased prevalence of DM.[6] This analysis was limited, however, to patients with ST-segment elevation myocardial infarction (STEMI) who were referred to cardiac catheterization, and did not specifically focus on DM-specific outcomes. Prior ARIC investigations have assessed the association of diabetes with one-year mortality in patients hospitalized with AMI. In the ARIC CHD community surveillance population of 13,068 weighted hospitalizations for AMI between 1987-1997, ~25% had diabetes. Age-adjusted gender- and race-specific odds ratios (OR) for 1-year case fatality comparing patients with vs. without DM were 2.0 (95% CI, 1.6–2.4) for white men and 1.4 (95% CI, 1.1–1.8) for white women. This analysis did not find a significantly increased risk amongst African-American patients.[7] However, the ARIC study has since accrued 17 years of community surveillance data (1998-2014), during which time the sample size of African American patients hospitalized with AMI has increased. Also of note, in 1997 the American Diabetes Association changed the recommended guidelines for definition of DM, by decreasing fasting glucose levels from 140 mg/dL to 126 mg/dL.[8] We propose to conduct a contemporary analysis of DM in patients who are hospitalized with AMI (both STEMI and non ST-segment elevation myocardial infarction [NSTEMI])from 2000-2014, examining temporal trends in clinical presentation, management, and outcomes, both overall and among demographic subgroups.

5. Main Hypothesis/Study Questions:

1. What is the prevalence of DM among patients hospitalized with AMI?
    - Has the prevalence of DM among AMI hospitalizations changed over time?
    - Do prevalence and temporal trends differ by demographic subgroups?
    - Do prevalence and temporal trends differ by type of MI (STEMI vs NSTEMI)?

2. Do the presenting features of patients admitted with AMI differ for patients with and without DM?

- Are patients with vs. without DM who have an AMI sicker on admission? (we will assess this by deriving the GRACE and TIMI risk scores). Do GRACE / TIMI risk scores differ over time or by demographic subgroups for patients with vs. without DM who are hospitalized for AMI?
- Are there differences in acuity of presentation (*ie*, onset of acute pulmonary edema / congestive heart failure, cardiogenic shock, ventricular fibrillation / cardiac arrest / asystole) for patients with vs. without DM? Does clinical acuity differ over time or by demographic subgroups for patients with vs. without DM?
- Are there differences in the presentation of acute chest pain / acute cardiac symptoms for patients with vs. without DM? Do presenting symptoms differ over time or by demographic subgroups for patients with vs. without DM who are hospitalized for AMI?
- Are there differences in the mode of arrival (by EMS vs not EMS) for patients with vs. without DM? Does mode of arrival differ over time or by demographic subgroups for patients with vs. without DM who are hospitalized for AMI?
- Are there differences in prevalent risk factors (*ie*, smoking, kidney function [derived from serum creatinine and CKD-Epi formula], stroke, hypertension) for patients with vs. without DM? Does the prevalence of risk factors differ over time or by demographic subgroups for patients with vs. without DM who are hospitalized for AMI?
- As a sensitivity analysis, do presenting features differ for patients with vs. without DM by type of AMI (NSTEMI vs. STEMI)?

3. Does clinical management differ for patients hospitalized with AMI with and without DM?

- Are there differences in utilization of evidence based therapies (*ie*, aspirin, antiplatelets, ACEi, lipid lowering medications, invasive angiography, percutaneous and surgical revascularization) for patients with vs. without DM? Does utilization of therapies differ over time or by demographic subgroups for patients with vs. without DM?
- As a sensitivity analysis, does clinical management differ for patients with vs. without DM by type of AMI (NSTEMI vs. STEMI)?

4. Do mortality outcomes differ for patients hospitalized with AMI with and without DM?

- Are there differences in short-term (30-day) and long term (1-year) mortality for patients with vs. without DM? Does mortality differ over time or by demographic subgroups for patients with vs. without DM?
- As a sensitivity analysis, do clinical course and mortality outcomes differ for patients with vs. without DM by type of AMI (NSTEMI vs. STEMI)?

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>Study Population:</u>

Patients hospitalized with AMI captured by the ARIC community surveillance between 1987-2014.

Exposure:
Patients hospitalized with classification of definite / probable AMI, with and without DM. As a sensitivity analysis we will also consider, ICD-9 discharge codes for AMI

Outcomes:

- Prevalence and trends in demographics, presenting features (acute pulmonary edema / congestive heart failure, cardiogenic shock, ventricular fibrillation / cardiac arrest / asystole), management, and outcomes of patients admitted with AMI stratified by presence of DM.
- 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
Because we are examining trends over time, we will exclude patients 75–85 years of age as this age group was only sampled between years 2005 to 2014.

Subgroup-Analysis:

We will perform a subgroup analysis comparing all-cause mortality in patients with vs without diabetes across the following subgroups:

- Age (<60 years & ≥60 years)
- Sex
- Race
- Prior history of heart failure
- Prior history of CKD
- Aspirin use
- Lipid lowering therapy use

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 3 days of hospitalization.

Medical Therapies

Medications were abstracted if administered either during hospitalization or prescribed at hospital discharge. Aspirin abstraction required routine rather than *pro re nata* administration. Non-aspirin antiplatelet therapy was abstracted 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 blocker abstracted included β_1 adrenergic antagonists. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ACEi/ARB) were abstracted 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

All statistical analyses will be carried out using SAS 9.4 (SAS Institute; Cary, NC). Statistical tests and models will be weighted by the inverse of the sampling probability and will account for the stratified sampling design. 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 Rao-Scott χ^2 tests.

Overall and subgroup-specific temporal trends in variables of interest (demographics, presenting features, management, and outcome variables) for patients with DM vs. those without DM will be visually plotted. Significance of trends will be analyzed by the Cochran-Armitage test for trend, using logistic regression (PROC surveylogistic) with year of admission regressed as an ordinal variable.

Overall and subgroup-specific relative probabilities of patients with vs. without DM receiving guideline-directed AMI medications (aspirin, other antiplatelets, beta blockers, and lipid-lowering medications) or undergoing invasive procedures (angiography and revascularization) will be derived from multivariable logistic regression, with odds ratios converted into relative risks (RR) and 95% confidence intervals (CI). Models will be adjusted for demographics, geographic region, and year of admission. As sensitivity analyses, we will also construct models stratified by demographic subgroups and by AMI type, and additionally adjust for acuity (acute heart failure / pulmonary edema, ventricular fibrillation, cardiac arrest, and cardiogenic shock; or alternatively, GRACE risk score).

Overall and subgroup-specific 30-day and 1-year all-cause mortality will be compared between patients with and without DM using multivariable logistic and Cox regression, respectively, adjusted for demographics, geographic location, and year of admission.

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)?

ms# 3022: *Racial trends in the management of acute myocardial infarction: The Atherosclerosis Risk in Communities (ARIC) Surveillance Study.* This manuscript was published in JAHA and includes many of the coauthors in the current proposal.

ms# 3105: *28-year Trends in the Incidence and Management of Acute Myocardial Infarction in the Young Adult Population (1987-2014).* This manuscript was published in Circulation and includes many of the coauthors in the current proposal

ms# 3063: *Management and outcomes of acute myocardial infarction with inpatient vs. outpatient onset.* This manuscript was published in JAHA and includes many of the coauthors in the current proposal.

ms# 528: *Is diabetes an independent risk factor for mortality after MI?* This manuscript was published in 2004 in Acta Diabetelogica

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. https://www.cdc.gov/diabetes/basics/type2.html

2. Preis SR, Hwang S-J, Coady S, et al. Trends in All-Cause and Cardiovascular Disease Mortality Among Women and Men With and Without Diabetes Mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation*. 2009;119(13):1728-1735. doi:10.1161/CIRCULATIONAHA.108.829176

3. Cavender M, Steg G, Smith S, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death (REACH Registry). *Circulation*. 2015;132:923-931. DOI: 10.1161/CIRCULATIONAHA.114.014796

3. Jacoby RM, Nesto RW. Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course and prognosis. *J Am Coll Cardiol*. 1992;20(3):736-744. doi:10.1016/0735-1097(92)90033-j

4. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World J Diabetes*. 2014;5(4):444-470. doi:10.4239/wjd.v5.i4.444

5. Krishnan U, Brejt J, Schulman, J, et al. Temporal trends in the clinical acuity of patients with ST-segment elevation myocaridal infarction. *American Journal of Medicine.* 2018;131: 100e9-100.e20.

6. Weitzman S, Wang C, Rosamond WD, et al. Is diabetes an independent risk factor for mortality after myocardial infarction? The ARIC (Atherosclerosis Risk in Communities) Surveillance Study. *Acta Diabetol*. 2004;41(2):77-83. doi:10.1007/s00592-004-0148-9

7. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183–97.