

## ARIC Manuscript Proposal #3192

PC Reviewed: 5/14/19  
SC Reviewed: \_\_\_\_\_

Status: \_\_\_\_\_  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a.Full Title:** Race and sex differences in recurrent AMI incidence in the 4 US communities

**b. Abbreviated Title (Length 26 characters):**

Differences in Recurrent MI

**2. Writing Group:**

Writing group members: Duygu Islek, Alvaro Alonso, Wayne Rosamond, Viola Vaccarino, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. DI **[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:**

The analysis is estimated to be completed in 2 years.

#### **4. Rationale:**

Acute myocardial infarction (AMI) fatality rates have declined over the last decade with the progress in primary and secondary prevention therapies (Chen J. *Circulation*. 2010;121:1322-1328). As a consequence, the population at risk of recurrent AMI are likely to increase.

Previous analyses have reported differences in AMI hospitalizations in terms of race and sex, with blacks experiencing lower declines in AMI hospitalizations than whites from 2002 to 2007 among Medicare fee-for-service beneficiaries (24.4% decline in white men versus 18.0% in black men; 23.3% in white women versus 18.4% decline in black women) (Chen J, *Circulation*. 2010;121:1322-1328). Rates of recurrent AMI hospitalizations are likely to parallel these trends. In fact, the ARIC Community Surveillance Committee Report (2005 to 2011) has shown temporal declines in rates of recurrent AMI for whites but an increase in blacks. The racial difference in trends seemed to be more prominent among women than among men (average annual percent change in rates per 10,000 persons in mortality due to recurrent AMI adjusted for age: 16.9% in black men vs -2.5% in white men; 25.4% in black women, vs -5.3% in white women) (Rosamond et al. ARIC Surveillance Committee Report, Community trends in the incidence of MI, mortality due to CHD, and case fatality for ARIC communities for event years 2005-2013).

A previous paper also reported an overall relative decline in recurrent AMI hospitalization rate by 27.7% in a national sample of 2,305,441 Medicare beneficiaries hospitalized for AMI from 1999 to 2010 in the US (Chaudhry S. *J Am Heart Assoc*. 2014;3: e001197). These declines primarily included older individuals which limits assessment of race-related disparities since blacks develop AMI earlier in life than whites. In contrast to the ARIC Surveillance Committee Report, this paper reported declines in trends of recurrent AMI hospitalization rates for both blacks and whites. However, the decline was less in black patients than in whites with a relative 27.7% decline in whites, from 11.9% (95% CI 11.8 to 12.1) to 8.6% (95% CI 8.5 to 8.8) versus a relative decline in blacks of 13.6%, from 13.2% (95% CI 12.6 to 13.8) to 11.4% (95% CI 10.9 to 12.0). The risk adjusted rates of annual decline in recurrent AMI hospitalization was also higher for whites compared to blacks (Chaudhry S et al. *J Am Heart Assoc*. 2014;3: e001197). Another study reported higher 5-year mortality rates in blacks vs whites among 30 day survivors of AMI and reported lower rates of revascularization treatment in blacks compared to whites but the study population was limited to patients enrolled in five large clinical trials (Mehta, R et al. *The American Journal of Medicine* (2006) 119, 70.e1-70.e8).

The black-white differences in incidence of recurrent AMI hospitalizations could be explained by difference in risk factors and higher rates of out-of-hospital AMI mortality in blacks. Also, considering the inconsistent published results on racial differences in recurrent AMI incidence and mortality, exploring differences in out-of-hospital mortality as part of our analysis of recurrent AMI incidence data, as well as case fatality, would help better understand recurrent AMI incidence and mortality differences according to race and sex.

In this proposal, we propose to analyze ARIC surveillance data for the period from 2005 to 2014 to investigate race disparities in recurrence of AMI.

The surveillance data has the unique aspect of being a large population-based sample, including approximately 470,000 residents aged 35-84. This will allow to examine the data in specific subgroups, such as sex, age, and study period. The data will also allow to differentiate out-of-hospital from in-hospital AMI recurrence mortality, which has rarely been examined before.

In the second proposal, we propose to comprehensively analyze ARIC cohort data for the entire period from 1987 to 2017 to investigate race disparities in recurrence of AMI. The cohort has several unique aspects that would provide strengths to this comprehensive analysis. First, the cohort will allow to analyze a 30 year period, which would provide additional insight to our proposed parallel analysis in the surveillance data (that only includes a period between 2005 and 2014). Second, the cohort data allows to include socioeconomic variables (such as income and education) in addition to risk factors such as history of hypertension, diabetes, and AMI severity to include in our models. Third, the cohort allows to identify whether the AMIs are first AMIs or subsequent events. This would allow to estimate the rate of recurrent events among those who had an initial AMI.

## **5. Main Hypothesis/Study Questions:**

Hypothesis 1- ‘

We aim to investigate race differences in the rate of recurrent AMI in the **ARIC surveillance** population aged 35-84 years in four U.S. communities between years 2005-2014. We hypothesize that blacks have a higher rate of recurrent AMI compared to whites. As secondary outcomes, we will examine race differences in in-hospital and out-of-hospital mortality rates of recurrent AMI.

Hypothesis 2-

We aim to investigate race differences in the rate of recurrent AMI among **ARIC cohort** participants who experienced a nonfatal AMI in the study period (1987-2016). As secondary outcomes, we will examine in-hospital and out-of-hospital mortality rates of recurrent AMI. We hypothesize that blacks have a higher incidence of recurrent AMI than whites, even after adjusting for socioeconomic and cardiovascular risk factors.

## **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).**

For Hypothesis 1, we will use the most updated **ARIC surveillance** data available in the interval 2005-2014. Community residents aged 35-84 years were considered eligible for surveillance in this interval (2005-2014). (Previously it was 35-74 years and was expanded to 35-84 years from 2005-2014). We will define recurrent AMIs as ‘any definite or probable recurrent AMI’ occurring in the surveillance population. The incidence rates (IRs) and 95% CIs of recurrent

AMI will be calculated and modeled with Poisson regression. The models will be constructed before and after adjusting for sex, history of hypertension, history of diabetes, smoking status and surveillance year. We will also stratify the data for sex to examine possible sex by race interactions. Models will account for the stratified sampling design and will be weighted by the inverse of the sampling probability; standard errors will be computed taking into account the sampling (Rosamond et al. *Circulation* 2012;125(15):1848-57). We will follow recommendations of the surveillance committee.

For hypothesis 2, we prepared a separate manuscript proposal. We will use the most updated **ARIC cohort** data available. We will first identify the population who had an AMI for the first time in the study period. Approximately 1,500 nonfatal AMIs were estimated from a recent publication with follow-up to 2013 (Mok T. et al. *J Am Heart Assoc.* 2018;7(4)); number of events will be higher with the additional available follow-up. Recurrent AMI incidence will be the main outcome, defined as any definite or probable recurrent AMI in this population (Myerson M et al. *Circulation.* 2009;119(4):503-14). Because AMI case fatality may affect recurrence rates, the associations of race with initial AMI case fatality will also be examined. As secondary outcomes, we will also examine in-hospital and out-of-hospital mortality rates of recurrent AMI.

The incidence rates (IRs) and 95% CIs of recurrent AMI per 1000 person-years will be calculated and modeled with Poisson regression, stratifying age by 5-year groups and calendar time by 5-year periods corresponding to the ARIC visit intervals.

We will use proportional hazard models constructed before and after adjusting for covariates age, sex, race/study site, education, age at incident AMI diagnosis, AMI severity, history of hypertension, history of diabetes, smoking status and income level. We will use the Death in Cardiac Disease Tool (PREDICT) score, which is an admission-day prognostic score for patients hospitalized for MI, developed by Jacobs et al (Jacobs D et al. *Circulation.* 1999;100:599–607.) and previously modified for ARIC (Watkins S et al *Am J Cardiol.* 2005;96:1349 –1355.) to create an indicator of AMI severity.

We will implement hierarchical models that progressively adjust for covariates. Starting from Model 1, age and calendar time period will be included. In model 2, we will additionally include sex, race/study site and education as demographic variables. In model 3, we will additionally include hypertension, diabetes, smoking status, and AMI severity as risk factors. We will adjust for all the covariates in the final model.

We will also stratify the data by sex to examine possible sex by race interactions.

We will exclude patients who are non-white and non-black, as well as non-whites in the Minnesota (MN) or Washington County sites. As a limitation in the cohort data, we recognize that all participants in Jackson site were black and all participants in the Minnesota and Maryland sites were white, therefore we will not be able to compare differences between whites and blacks independently of the differences that exist between study sites. Therefore, we plan to create the following 5 groups and compare the recurrent AMI rates across them: whites in MN, whites in Washington County, whites in Forsyth County, blacks in Forsyth County, blacks in Jackson. We will also exclude those without a baseline history of AMI.

All analyses will be conducted using SAS statistical software version 9.4.

7.a. Will the data be used for non-CVD analysis in this manuscript?  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  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.csc.unc.edu/ARIC/search.php>

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)?

Wayne D. Rosamond et al 'Twenty-Two-Year Trends in Incidence of Myocardial Infarction, Coronary Heart Disease Mortality, and Case Fatality in 4 US Communities, 1987–2008' DOI: 10.1161/CIRCULATIONAHA.111.047480

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  Yes  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.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](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](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript \_\_\_\_ Yes  No.