ARIC Manuscript Proposal #2098

PC Reviewed: 5/24/13 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Temporal trends in mortality associated with atrial fibrillation complicating acute myocardial infarction

b. Abbreviated Title (Length 26 characters):

Atrial fibrillation with myocardial infarction

2. Writing Group:

Writing group members: Alvaro Alonso, Lin Chen, Pamela Lutsey, Alanna Chamberlain, Sue Duval, Erin Michos, Eric Whitsel and Wayne Rosamond

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

First author: **Lindsay Smith**
Address: West Bank Office Building
1300 South Second Street, Suite 300
Minneapolis, MN 55454

Phone: 612-624-5238 Fax: 612-624-0315
E-mail: smit4430@umn.edu

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).
Name: Alvaro Alonso
Address: West Bank Office Building
1300 South Second Street, Suite 300
Minneapolis, MN 55454

Phone: 612-626-8597 Fax: 612-624-0315
E-mail: alonso@umn.edu

3. Timeline: This proposal is part of a dissertation thesis and work will begin in early 2013 and should be completed by the fall of 2013.

4. Rationale:

In the 1980's and 1990's the incidence rate of acute myocardial infarction (AMI) in the United States (US) was fairly stable.[1-4] However, since the beginning of the 21st century, the rate has declined significantly.[5-7] Regardless of this encouraging trend, the estimated annual incidence of AMI in the US remains high at 610,000 cases.[8]

Atrial fibrillation (AF), the most common cardiac arrhythmia, often coexists with AMI.[9] The presence of AF is associated with a significantly increased risk of death among AMI patients; the mortality odds ratio associated with AF was 1.46 (95% confidence interval [CI] 1.35 – 1.58), as reported in a recent meta-analysis of published studies.[10] The increased risk of mortality remained regardless of the timing of AF (diagnosed prior to or during index hospitalization) and was robust to adjustment for confounding factors.[10]

Understanding temporal trends in the occurrence of AF in the setting of AMI is relevant given the common co-occurrence of these conditions, as is determining whether the impact of AF on AMI prognosis has changed over time. Better understanding of the temporal trends could facilitate identification of a more vulnerable population or unmet treatment needs. Despite the importance of this topic, there is a dearth of data on temporal trends related to the association of AF with the prognosis of AMI patients. The Worcester Heart Attack Study examined 15-year trends (1990 – 2005) in AMI patients with new-onset AF during index AMI hospitalization. During each of the years under study, the mortality rate in-hospital, at 30-days and at 1-year post-discharge, was significantly higher among AMI patients who developed AF compared to those who did not after controlling for potential confounders.[11] In-hospital mortality among AMI patients without AF decreased steadily from 1990 to 2005 (12.8% in 1990 to 5.9% in 2005), but decreased only slightly among those with AF (24.6% in 1990 to 21.3% in 2005). [11] There was no significant change during the study period in the multivariable adjusted odds of dying at 30-days or 1-year post-discharge.[11] The multivariable adjusted odds ratio of 1-year mortality in those who developed AF during hospitalization for AMI in 2005 compared to 1990 was 0.77 (95% CI: 0.34 – 1.76).[11] A population-based study from 1983 – 2007 among patients hospitalized for incident AMI in Olmsted County, MN included patients with and without diagnosed AF at the time of their incident AMI.[12] AF, regardless of its timing, was associated with an increased risk of death.[12] There was no clinically relevant modification of the association between AF and mortality by age, sex or calendar year of incident AMI.[12]

These previous studies, however, lacked geographical and racial diversity, and their power to detect significant trends over time was limited given their sample size. Therefore, we propose to explore 20-year trends in the association of AF with mortality in AMI patients using data from the community surveillance component of the ARIC Study.

5. Main Hypothesis/Study Questions:

We hypothesize that all-cause mortality among AMI patients without AF has significantly improved over time, while all-cause mortality among patients with co-

occurring AMI and AF has remained constant. Additionally, we hypothesize that, among those who had AF, overall survival has improved more over time among men and whites compared to women and African Americans, respectively.

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).

The community surveillance component of ARIC will be utilized to address this study question. Hospitalization with first incident definite or probable AMIs will be eligible for inclusion.

AF status during hospitalization for AMI will be identified through hospital discharge codes (ICD-9 code 427.3, 427.31 or 427.32 or an ICD-10 code of I48).

The outcome of interest is all-cause mortality in-hospital, at 30-days and 1-year post discharge.

Statistical analysis

Population characteristics for the four ARIC communities as well as patient specific characteristics will be presented. Poisson regression will be used to calculate rates of AMI hospitalization with and without concomitant AF in each ARIC community, adjusted for age group, sex, race and community.

Trends in the association of AF with mortality among AMI patients will be examined by including an interaction term for AF status and calendar year (AF * year) in a logistic regression model with calendar year of AMI hospitalization as the independent variable, modeled as a continuous variable, and number of deaths as the dependent variable, adjusted for age group, sex and race. Analyses will be repeated including a quadratic term for time ($year^2$) to assess the presence of nonlinear trends. In addition, restricted cubic splines will be used to explore nonlinear associations. The models will be adjusted for medication use and presentation characteristics (heart rate, systolic blood pressure), as recorded in the adjudication forms.

In an analysis restricted to those with AF, potential effect modification of trends in overall survival by sex or race will be assessed by including 2-way interaction terms (sex * year and race * year) in the logistic regression model; effect modification by AMI severity, using the continuous Predicting Risk of Death in Cardiac Disease Tool (PREDICT) score, will be tested with a linear regression model including an interaction term (PREDICT * year). The PREDICT score, developed in the Minnesota Heart Survey, a community-based study, uses information routinely collected during AMI hospitalization to determine clinical severity and long-term (6-year) mortality risk.[13] A $P < 0.10$ will be considered evidence of statistically significant effect modification and, if present, stratified analyses will be performed.

A subgroup analysis among patients undergoing cardiac operative procedures will be performed. AF following cardiac operative procedures is fairly common[14] and known to increase the risk of in-hospital and long-term mortality.[15] Therefore, a subgroup analysis will be performed among AMI patients who had heart revascularization (ICD-9 code 36.X) or other cardiac surgery involving heart valves or septa (ICD-9 code 35.X)

during the index hospitalization to determine if the trend in the association with prognosis is the same.

Analyses will be weighted by the inverse of the sampling fraction and standard errors will be computed by stratified random sample methodology to account for the complex sampling scheme. Analyses will be conducted using the survey procedures in SAS (version 9.2; SAS Institute, Inc, Cary, NC) and rates will be calculated using SUDAAN (Research Triangle Institute, Research Triangle Park, NC).

Limitations

First, the timing of AF is unknown and therefore cannot be classified as incident or recurrent. However, a previous study showed that the occurrence of AF at any time following AMI is associated with a significantly increased risk of death (HR: 3.77; 95% CI: 3.37 – 4.21) and the increased risk of death was similar among patients with AF preceding AMI.[12] Second, patients who develop AF after they have been discharged from the hospital will be misclassified. However, there is a positive association between increasing time from incident AMI to first-detected AF and risk of death; consequently, the association likely would be underestimated.[12] Third, community residents hospitalized outside of the study catchment area will be missed unless they were transferred to and discharged from a hospital within the surveillance area. Despite this limitation, the number of missed events is small.[16] Fourth, the ARIC Mortality and Morbidity Classification Committee adjudicates AMI diagnoses but not AF diagnoses. However, hospitalization discharge codes are useful for identifying AF patients.[17] Fifth, coding practices might have changed over time, with AF in the setting of AMI coded less frequently in the earlier years. In an effort to quantify the impact of changes in coding practice, the average number of ICD codes per hospitalization will be calculated and compared over time. If the average number of ICD codes per hospitalization has increased over time, the analyses will be repeated adjusting for the number of ICD codes.

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 ICTDER03 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)?

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.

References

1. Roger VL, Jacobsen SJ, Weston SA, et al. Trends in the incidence and survival of patients with hospitalized myocardial infarction, Olmsted County, Minnesota, 1979 to 1994. *Ann Intern Med.* Mar 5 2002;136(5):341-348.

2. Goldberg RJ, Yarzebski J, Lessard D, Gore JM. A two-decades (1975 to 1995) long experience in the incidence, in-hospital and long-term case-fatality rates of acute myocardial infarction: a community-wide perspective. *J Am Coll Cardiol.* May 1999;33(6):1533-1539.

3. Rosamond WD, Chambless LE, Folsom AR, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. *N Engl J Med.* Sep 24 1998;339(13):861-867.

4. McGovern PG, Pankow JS, Shahar E, et al. Recent trends in acute coronary heart disease--mortality, morbidity, medical care, and risk factors. The Minnesota Heart Survey Investigators. *N Engl J Med.* Apr 4 1996;334(14):884-890.

5. Rosamond WD, Chambless LE, Heiss G, et al. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987-2008. *Circulation.* Apr 17 2012;125(15):1848-1857.

6. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med.* Jan 2011;124(1):40-47.

7. Roger VL, Weston SA, Gerber Y, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation.* Feb 23 2010;121(7):863-869.

8. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation.* Jan 3 2012;125(1):e2-e220.

9. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J.* May 2009;30(9):1038-1045.

10. Jabre P, Roger VL, Murad MH, et al. Mortality associated with atrial fibrillation in patients with myocardial infarction: a systematic review and meta-analysis. *Circulation.* Apr 19 2011;123(15):1587-1593.

11. Saczynski JS, McManus D, Zhou Z, et al. Trends in atrial fibrillation complicating acute myocardial infarction. *Am J Cardiol.* Jul 15 2009;104(2):169-174.

12. Jabre P, Jouven X, Adnet F, et al. Atrial fibrillation and death after myocardial infarction: a community study. *Circulation.* May 17 2011;123(19):2094-2100.

13. Jacobs DR, Jr., Kroenke C, Crow R, et al. PREDICT: A simple risk score for clinical severity and long-term prognosis after hospitalization for acute myocardial infarction or unstable angina: the Minnesota heart survey. *Circulation.* Aug 10 1999;100(6):599-607.

14. Ommen SR, Odell JA, Stanton MS. Atrial arrhythmias after cardiothoracic surgery. *N Engl J Med.* May 15 1997;336(20):1429-1434.

15. Villareal RP, Hariharan R, Liu BC, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol.* Mar 3 2004;43(5):742-748.

16. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol.* Feb 1996;49(2):223-233.

17. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J.* Jul 2009;158(1):111-117.