ARIC Manuscript Proposal #3168

PC Reviewed: 5/14/19 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Atrial Fibrillation in Patients with Mitral Regurgitation Admitted with Heart Failure in the ARIC Community Surveillance: Prevalence, Correlates, and Impact on Outcomes

b. Abbreviated Title (Length 26 characters): Valvular heart failure

2. Writing Group:

Writing group members: Sameer Arora MD, Patricia Chang MD MHS, Lin Y Chen MD MS, Alvaro Alonso MD PhD , Wayne D. Rosamond PhD, Elsayed Soliman MD, MSc, MS, John P Vavalle MD MHS, others welcome.

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

F**irst author**:   **Sameer Arora**
Address:
    Division of Cardiology
    160 Dental Circle
    CB # 7075
    Chapel Hill, NC 27599-7075
    Phone: 919-966-5201   Fax: 919-966-1743
    E-mail: saror@email.unc.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: Patricia Chang MD MHS
Division of Cardiology
University of North Carolina
Chapel Hill, NC 27599
Email: patricia_chang@med.unc.edu

3. Timeline:

Analysis completed within 3 months of approval of manuscript proposal, with manuscript drafted approximately 6 months later (November 2018).

4. Rationale:

Atrial fibrillation (AF) is the most common sustained arrhythmic disorder and is associated with poor prognosis (1). The link between AF and valvular heart disease, is well known (2,3). However, large studies evaluating the prevalence and impact of the presence of AF in patients with MR (mitral regurgitation) and aortic stenosis (AS) remain sparse. In a small study involving 360 patients with MR due to flail leaflets, almost half of the patients developed AF at 10 years and the presence of AF was independently associated with adverse cardiac events (4). Also, pre-operative AF in patients undergoing surgical mitral valve repair for degenerative MR had worse postoperative outcomes (5,6). MR and AS are the most common disorder in patients admitted with heart failure (HF). To our knowledge, studies investigating the prevalence of AF in functional MR and AS are limited. Therefore, we thought to use data from the ARIC community surveillance to investigate the prevalence of AF in patients admitted with HF and moderate to severe valvular disease on echocardiogram. Furthermore, we will also investigate the impact of AF on outcomes in these patients.

5. Main Hypothesis/Study Questions:
1. Among patients hospitalized with HF in the ARIC surveillance, what is the prevalence of AF? How does this prevalence differ in systolic and diastolic HF?
2. How does the prevalence of AF differ among those with moderate to severe valvular disease (MR and AS) hospitalized with HF, stratified by systolic and diastolic HF? How does the prevalence of MR compare to that of all patients hospitalized with HF? How does the prevalence of AF in moderate to severe AF compare to that of those with mild or no degree of valvular disease?
3. In the community HF population with moderate to severe valvular disease (MR and AS), what are the differences in clinical characteristics between patients with AF and those without AF? We speculate that those with AF are sicker and at a later stage of valvular disease.
4. What is the impact of AF on length of stay, all-cause in-hospital, 28-day, and 1-year mortality? We hypothesize that mortality may be worse for those with AF, even after adjusting for confounders.
5. Among ARIC surveillance participants who were hospitalized with HF with moderate to severe MR and AS, what is the impact of AF on rate of readmissions?

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 design:
This study will be based on all HF hospitalizations from the ARIC community surveillance study till date. The study will be limited to those hospitalized for HF with information available on AF status. To evaluate the prevalence of AF in valvular disease admitted for HF, those with available echocardiographic data will be included. Those with missing valvular disease status will be excluded.

Ascertainment of AF: by either of these 2 criteria

1. Extracted history of AF by trained extractors from medical records which includes use of physician notes (variable 11b)
2. ICD 9 coding for AF in discharge diagnosis (CHIA form, question 2a onwards)
3. Sensitivity analysis will also be conducted from ECGs abstracted for which AF on ECG or Telemetry as a variable is captured (HFS form, Version C, variable 26c or 26c1)

Key Variables of Interest:
1. MR and AS in hospitalized HF.
2. Heart failure specifics: left ventricular ejection fraction, acute decompensated heart failure (ADHF), heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and chronic stable heart failure (csHF)
3. Demographics: Age, race and gender
4. Comorbidities: Hypertension defined as ≥140/90 or taking antihypertensive medication, diabetes, COPD, renal failure, hyperlipidemia, coronary artery disease
5. Other clinical characteristics: body mass index (BMI), smoking history and length
6. History of valve surgery (variable HF 11e3)

Outcomes and Data Analysis:
We will describe the prevalence of AF in patients hospitalized with HF and with MR and AS on echocardiogram sampled by the ARIC community surveillance study. AF will be ascertained as mentioned above. We will compare outcomes between the AF and the non-AF group. Length of hospital stay, in-hospital, 28-day, and 1-year mortality will be our longitudinal outcomes. We will also evaluate 30-day and 1-year rehospitalizations.

Analyses will be weighted by the sampling fraction and will account for the stratified sampling design. Analysis of variance and Rao-Scott chi-square tests will be used to compare demographic and clinical covariates. In-hospital, 28-day, and 1-year mortality will be assessed by multivariable logistic regression. Among community participants with hospitalized heart failure, number of re-hospitalizations over a 30-days and 1-year will be analyzed by multivariable Cox regression, using robust sandwich estimators to account for correlation between repeat events. Age-adjusted trends will be reported as average annual percent change by race and sex, using Poisson regression for first and recurrent hospitalization rates and using logistic regression for case fatality. Mean length of hospital stay contrasting AF to non-AF will be analyzed using multiple linear regression.

Limitations and challenges:
With the available data, several limitations may be present within this study. This study will be limited to patients with available echocardiography abstractions and with MR and AS on echocardiography. Patients may be counted more than once if they present to a hospital and are entered into a study multiple times over the years. The echocardiography data is based on real-world clinical reports, and is subject to variations in measurement and interpretation, as well as

differences in imaging protocols, equipment, and sonographers. Finally, ascertainment of AF by the above used criteria has its own limitations. However, by utilizing extracted history of AF along with ICD coding should strengthen the evidence of presence of AF.

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)?

1. MP# 2089: Susan Cheng, et al . Contemporary Burden of Valvular Disease in the Community.
    Our aim is different in this study

2. MP# 529: M, Eigenbrodt, et al. Distribution and associations of valvular lesions in the Jackson ARIC Cohort.
    Our study has a different aim

3. MP# 1158: John J King, et al. Prevalence and correlates of mitral, tricuspid, and aortic regurgitation in middle-aged and elderly African-Americans: the ARIC study.
    Our aim is different
4. MP# 2692: Sola et al. The Clinical Characteristics and Outcomes of Patients with Valvular Heart Disease Admitted to the Hospital with Heart Failure: an ARIC Communities Study

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.   Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB and Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946-52.
2.   Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994;89(2):724-30.
3.   Vasan RS, Larson MG, Levy D, Evans JC, Benjamin EJ. Distribution and categorization of echocardiographic measurements in relation to reference limits: the Framingham Heart Study: formulation of a height- and sex-specific classification and its prospective validation. Circulation. 1997;96(6):1863-73.
4.   Grigioni F, Avierinos JF, Ling LH, Scott CG, Bailey KR, Tajik AJ, et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. J Am Coll Cardiol. 2002;40(1):84-92.
5.   Alexiou C, Doukas G, Oc M, Oc B, Swanevelder J, Samani NJ and Spyt TJ. The effect of preoperative atrial fibrillation on survival following mitral valve repair for degenerative mitral regurgitation. *Eur J Cardiothorac Surg*. 2007;31:586-91.
6.   C.M. Tribouilloy, M. Enriquez-Sarano, H.V. Schaff, *et al.*Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. irculation, 99 (1999), pp. 400-405