ARIC Manuscript Proposal #2692

PC Reviewed: 1/16/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Clinical Characteristics and Outcomes of Patients with Valvular Heart Disease Admitted to the Hospital with Heart Failure: An ARIC Communities Study

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

2. Writing Group:

Writing group members: Michael Sola, Aamir Husain, John Vavalle, Michael Yeung, Cassie Ramm, Melissa Caughey, Amil Shah, Patty Chang, Kunihiro Matsushita, Dalane Kitzman, 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]**

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3. Timeline:

Analysis completed within 3 months of approval of manuscript proposal, with manuscript drafted approximately 3 months later (June 2016).

4. Rationale:

Heart failure currently represents one of the most common causes of both hospitalizations and mortality in those over 65, with more than 650,000 cases diagnosed annually.[1] Valvular heart disease plays a major role in the development of heart failure, and its significance as a contributing factor to heart failure is increasing as the US population continues to age.[2] The prevalence of valvular heart disease in patients 65-75 years old and those > 75 years old is 4.4% and 11.7%, respectively. [3] By 2030, the population of patients 65 years old and older is expected to grow by 5.7%, comprising 20.6% of the total population. With this growth in the older population, a significant increase in the burden of valvular heart disease and its resultant heart failure is expected. [4]

Severe valvular heart disease can lead to significant heart failure symptoms, and ultimately death. For example, aortic stenosis is one of the most common acquired valvular defects in the developed world, affecting approximately 2% of the population over 65. [5] Typically, this is due to the deposition of calcium associated with aging and leads to a pressure overload of the left ventricle resulting in congestion and heart failure. Medical therapy may provide symptom relief, but it is ineffective in the treatment of aortic stenosis. The only effective treatment for aortic stenosis is valve replacement. [6]

Beyond aortic valve disease, mitral valve disease represents an even larger contributor to heart failure. Mitral regurgitation is the most common valvular lesion associated with heart failure, as its incidence approaches roughly 9% in those over age 75.[7] Importantly, mitral regurgitation has been demonstrated to be an independent predictor of 5 year mortality in patients with heart failure. [8]

The long-term prognosis of valvular heart failure is dismal. Depending on symptom severity, the estimated 5-year mortality is >20% per year in patients with aortic and mitral regurgitation and 20% and 44% in those with aortic and mitral stenosis, respectively [9, 10, 11]

As the prevalence of valvular disease and heart failure continue to grow, it is important to understand the characteristics and prognostic factors of patients with heart failure and valvular heart disease. With this ARIC proposal, we will describe the prevalence and type of aortic and mitral valvular disease in patients hospitalized with heart failure, and analyze associations with length of hospital stay, rehospitalization, and mortality.

References

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5. Main Hypothesis/Study Questions:

1. Among patients hospitalized with heart failure in the ARIC communities surveillance study, what is the prevalence of moderate or severe left heart valvular disease; namely, aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis (MS), or mitral regurgitation (MR)?
2. How do heart failure patients with different types of valvular heart disease differ by demographic and clinical characteristics (ex. AS vs. AR vs. MS vs. MR vs. none)?
3. How does all-cause in-hospital, 28-day, and 1-year mortality differ by the various types of valvular heart disease and heart failure and those with heart failure free of valvular disease? We hypothesize that mortality will differ by ejection fraction, aortic vs. mitral valve disease, and by stenotic vs. regurgitant valve disease.
4. Is the prognosis different for patients with heart failure with preserved ejection fraction and valvular heart disease as compared to those with heart failure with reduced ejection fraction and valvular heart disease?
5. Do patients with valvular heart disease admitted with heart failure have longer lengths of ICU stay, total hospital stay, and more procedures and/or testing, such as cardiac catheterization, echocardiograms, pulmonary artery catheter insertion, heart valve replacement, and cardiac surgery, as compared to patients without valvular heart disease admitted with heart failure? Our hypothesis is that patients with heart failure and valvular heart disease who are admitted with acute decompensated heart failure will have longer lengths of hospital stay and more testing/procedures, than those without valvular heart disease.
6. Among ARIC Cohort members who were hospitalized with heart failure, what is the rate of readmissions, compared to those without valvular heart disease? We hypothesize that those with valvular heart failure will have higher readmission rates.

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 heart failure hospitalizations sampled by the ARIC community surveillance study from 2005 to 2013. We will analyze admission for both chronic stable heart

failure and acute decompensated heart failure, but focus on outcomes related to acute decompensated heart failure. The prevalence and severity of valvular disease will be determined by echocardiography, limiting our study population to those with available echocardiography data. Because medical records for ARIC cohort members were also abstracted for each hospitalization, if hospitalized, we will also use the first hospitalization for cohort members with available echocardiography data as the study entry.

Key Variables of Interest:

1. Valvular heart disease: aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation
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, gender, socioeconomic status.
4. Comorbidities: Hypertension defined as ≥140/90 or taking antihypertensive medication, diabetes, COPD, renal failure, hyperlipidemia, CAD
5. Other clinical characteristics: BMI, smoking history and length

Outcomes and Data Analysis:

We will describe the prevalence and type of valvular heart failure in hospitalized heart failure patients sampled by the ARIC community surveillance study. We will also examine overall and stratified [(aortic vs mitral), (stenosis vs. regurgitation), (aortic or mitral vs. none)] associations with demographics and comorbidities. Longitudinal outcomes will include length of hospital stay, in-hospital, 30-day, and 1-year mortality. In the subset of ARIC cohort members hospitalized for heart failure, 30-day and 1-year rehospitalizations will be examined.

All analyses will be weighted by the sampling fraction and will account for the stratified sampling design. Demographic and clinical covariates will be compared using analysis of variance and Rao-Scott chi-square tests. In-hospital, 28-day, and 1-year mortality will be assessed by multivariable logistic regression. Among ARIC cohort members 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. Mean length of hospital stay contrasting valvular to non-valvular heart failure 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. There may also be a substantial number of patients with multiple valvular lesions (aortic and mitral, or stenosis and regurgitation) which will limit our ability to define isolated valvular heart disease. If this proves to be true, we will analyze patients with combined valvular heart disease. Patients may be counted more than once if they present to a hospital and are entered into a study multiple times over the years. Finally, 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.

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.
    a. This proposal was for the Cohort data for Visit 5 while our proposal is for the community surveillance data. Dr. Amil Shah is a coauthor for this manuscript proposal as well as our proposed one.

2. MP# 529: M, Eigenbrodt, et al. Distribution and associations of valvular lesions in the Jackson ARIC Cohort.
    a. This is also for the cohort data.

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.
    a. This is looking specifically at the Jackson cohort data, not the community data.

4. MP# 2528: Shah, Amil. Prognostic Value of Heart Failure Self-Report in the Community: The ARIC study.
    a. This study does not look at the specifics of valvular disease within heart failure patients.

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.