ARIC Manuscript Proposal #2807

PC Reviewed: 08/09/16   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Valvular diseases and long-term prognosis among African Americans in the community

  b. Abbreviated Title (Length 25 characters): Valve disease and CV outcomes

2.   Writing Group:
        Writing group members:

Jonathan Rubin, MD MHS; Amil Shah, MD; Ajay Kirtane MD, SM; Susheel Kodali, MD; Elizabeth Selvin, PhD, MPH; Alvaro Alonso, MD, MPH; Martin B Leon, MD; Scott Solomon, MD, MPH; Josef Coresh, MD, PhD; Ervin Fox, MD, MPH, Kunihiro Matsushita, MD, PhD others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. <u>JR</u> **[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: Analysis is to start as soon as manuscript proposal is approved. We plan to submit the manuscript for ARIC review <6 months from approval / data availability.

4.   Rationale:
The prevalence of valvular diseases in the United Sates has been estimated to be 2-3% after standardization of age and sex[1]. With an increasingly elderly population, the number of persons with valvular disease is expected to increase considerably. In addition to the increasing prevalence of valvular disease, there has also been a renewed interest in valvular disease with the introduction of novel percutaneous therapeutic alternatives, such as transcatheter aortic valve replacement (TAVR) for the treatment of aortic stenosis[2] and a variety of technologies aimed at treating mitral regurgitation[3].

Unfortunately, most studies of patients with valvular diseases originate from patients with advanced valvular disease who are referred for medical or surgical therapy[4-7]. As a result, there is limited information on the impact of valvular disease in the general population. Therefore, the ARIC study visit 3 will provide a population-based sample in which to comprehensively assess the relationship between valvular diseases and long-term cardiovascular outcomes.

5.   Main Hypothesis/Study Questions:

Each valvular condition (aortic stenosis and regurgitation, mitral stenosis and regurgitation, and tricuspid regurgitation) will be associated with adverse cardiovascular outcomes (described below).

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 methodological limitations or challenges if present).

Study design: Prospective follow up with visit 3 as baseline

Inclusions
All ARIC African American subjects from Jackson with echocardiogram data during visit 3 (n ≈ 2,400).

Exclusions:
Missing echocardiogram during visit 3, or missing covariates of interest.

Exposure:
Valvular disease was ascertained from echocardiograms read by one cardiologist specializing in echocardiography at the core reading center using an off-line image digital analysis system (Freeland Systems Cine View, Westfield, IN). The quality control measures for echocardiography during the third examination have been previously described[8, 9].

Regurgitant Lesions:
Severity of AR was based on the ratio of the proximal jet height to the LV outflow tract height. Aortic regurgitation severity was classified as trace (≤5%), mild (N5% but ≤24%), moderate (≥25 but ≤46%), and severe (≥47%) as previously described[9].
Severity of MR, TR and PR was based on the ratio of regurgitant jet area to atrial area. Mitral regurgitation, TR and PR severity were classified as either none, trace (≤5%), mild (N5% but ≤20%), moderate (N20% but ≤40%), or severe (N40%)

Stenotic Lesions:
Aortic and mitral leaflets were qualitatively assessed as previously described [10, 11] and categorized as minimal or no sclerosis, sclerosis and stenosis.

According to number of cases, we may combine a few severity categories in the analysis. Each of valvular lesions will be assessed separately at first; then their combinations will be assessed.

Outcomes:
- All-cause mortality
- Cardiovascular mortality
- Hospitalizations
- Incident heart failure hospitalizations (will also perform analysis for heart failure with preserved ejection fraction)
- Incident atrial fibrillation
- Incident ischemic stroke

<u>Statistical Analysis</u>
We will calculate the prevalence of each valvular disease by age and sex and explore baseline characteristics across categories of valvular lesions (e.g., none, mild, moderate, and severe). We will use Poisson regression to estimate the overall and the age and sex adjusted rates of our outcomes of interest and compare across each valvular disease. We will then use Cox proportional hazards models to explore the association of each valvular disease with outcomes of interest. Model will be initially adjusted by age and gender, and will then include smoking status, body mass index, waist-hip ratio, blood pressure, hypertensive medication use, diabetes, education, triglycerides, HDL and LDL cholesterol, lipid lowering medications, kidney function (estimated GFR from serum creatinine during ARIC visit 2) and prevalent CVD (CHD, HF, stroke).

We will formally test for effect modification by age, gender, and the presence/absence of history of cardiovascular disease (coronary heart disease, heart failure, or stroke).

<u>Limitations</u>
Echocardiograms were only available from participants from the Jackson site during visit 3. Despite adjustment for known risk factors for cardiovascular disease, we will not be able to rule out the possibility of residual confounding in the interpretation of our results.

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)?

   # 529   Distribution and associations of valvular lesions in the Jackson ARIC cohort. Eigenbrodt

   # 1158   Prevalence and correlates of mitral, tricuspid, and aortic regurgitation in middle-aged and elderly African-Americans: the ARIC study.   King

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/

12. 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.

References

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