ARIC Manuscript Proposal #2089

PC Reviewed: 3/12/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Contemporary Burden of Valvular Disease in the Community

b. Abbreviated Title (Length 26 characters):

Burden of Valvular Disease

2. Writing Group:
Writing group members:

Susan Cheng, Amil Shah, Brian Claggett, Hicham Skali, Patrick O'Gara, Scott Solomon, and OTHERS WELCOME

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __SC__

First author: Susan Cheng
Address: Brigham and Women's Hospital
Cardiovascular Division
75 Francis Street, PBB-1 North
Boston, MA 02115

Phone: 617-595-7127 Fax: 617-812-0425
E-mail: scheng3@partners.org

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: Scott Solomon
Address: Brigham and Women's Hospital
Cardiovascular Division
75 Francis Street
Boston, MA 02115

Phone: 857-307-1960 Fax: 857-307-1944
E-mail: ssolomon@rics.bwh.harvard.edu

3. Timeline: Analyses to begin Spring 2013.
A manuscript draft is expected during Summer 2013 / Fall 2013.

4. Rationale:

Compared to more common cardiovascular diseases, such as coronary heart disease and heart failure, relatively little is known about the epidemiology of valvular heart disease. Previous epidemiologic studies indicate that the overall prevalence of valvular heart disease in the population is less than 3%.[1,2] However, as shown in a study that pooled data from several cohorts including the Jackson Heart Study subset of the Atherosclerosis Risk in Communities (ARIC) Study, the prevalence of clinically significant aortic and mitral valve diseases substantially increases with age – approaching 12-14% in persons 75 years or older.[3] Prevalence of either aortic or mitral valve diseases appears slightly greater in men compared to women.[3] Whereas prior studies suggest that the prevalence of aortic calcific valvular disease is relatively similar between racial/ethnic groups in the United States,[4] there is little data on racial/ethnic differences for other common valvular lesions. Cross-sectional studies suggest that risk factors for aortic sclerotic or stenotic valve disease are similar to those for atherosclerosis.[4] However, risk factors for other degenerative valve disorders are not well established. Therefore, we propose to conduct a comprehensive and contemporary study of the prevalence of valvular heart disease in the total ARIC study sample with echocardiography at Visit 5. This study would include investigating both clinical and echocardiographic correlates of valve disease, in addition to the association of prevalent valvular disease with antecedent risk factor exposure.

5. Main Hypothesis/Study Questions:

Our main hypothesis is that while increased age is an important clinical correlate of prevalent valvular heart disease, certain risk exposures such as antecedent hypertension also contribute substantially to the presence of valve disease – and, particularly, valve disease with echocardiographic markers of associated cardiac remodeling.

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 study sample will include individuals who attended the ARIC Visit 5 examination, who underwent echocardiography at this visit.

Dependent variables. The primary dependent variables of interest will include presence of at least mild severity aortic stenosis, aortic regurgitation, mitral regurgitation, and mitral stenosis. We will also consider presence of at least moderate severity (i.e. clinically significant) valve disease, and all gradings of severity will be based on guidelines recommendations.[5-7] Re-adjudication of certain types and/or severity of valve disease will be performed where necessary (e.g. for mitral stenosis, which is not currently captured in the standard echo report).

Secondary outcomes will include presence of valve disease with features of associated cardiac remodeling, including increased LV end-diastolic diameter, LV wall thickness, LV mass, LV relative wall thickness (LV wall thickness divided by LV end-diastolic diameter), left atrial volume, and aortic root diameter. Presence of each remodeling index will be considered as a value in the upper quartile of age- and sex-adjusted values for each index.

Independent variables. The primary independent variables of interest will include: age, sex, race, body mass index, blood pressure (BP) components (SBP, DBP, PP, and MAP), prevalent hypertension (BP ≥140/90 mmHg or taking anti-hypertensive medication), diabetes, smoking status, total/HDL cholesterol ratio, and eGFR.

Additional independent variables of interest will include variables that capture antecedent burden of risk exposure, including: time-averaged BP measures (SBP, DBP, PP, and MAP) from visits 1 through 5 (with and without imputed BP values based on concurrent anti-hypertensive medication use[8]), and total years with documented hypertension since visit 1 (with and without anti-hypertensive treatment); time-averaged total/HDL cholesterol (with and without cholesterol-lowering treatment) and total years with documented hypercholesterolemia (total cholesterol >200 mg/dL or taking lipid-lowering treatment); total years of documented antecedent smoking; time-averaged body mass index, and total years with documented obesity, time-averaged fasting glucose, and total years with documented diabetes; and, time-averaged eGFR.

Analytical approach. We will perform initial descriptive analyses including unadjusted analyses of the relations between each of the independent variables with the dependent variables. We will then perform multivariable adjusted regression analyses to examine the association of independent variables with measures of diastolic function (primarily outcome variables: presence of aortic stenosis; presence of aortic regurgitation; presence of mitral regurgitation; presence of mitral stenosis). Relative contributions of independent variables to presence of each outcome variable will be evaluated using the partial R^2 value for each term in the model, in addition to a calculated population attributable risk percent for covariates that may be dichotomized (using validated methods[9]). The relative contributions of prevalent and antecedent burden of risk exposures will be evaluated in separate models.

Secondary analyses. In secondary analyses, we will use multiplicative interaction terms to assess for effect modification by age, sex, race, and hypertension status. We will perform stratified analyses for any covariates demonstrating significant effect modification. Whereas LV relative wall thickness is a continuous measure of LV geometry, we will also consider conducting analyses using categorical definitions of LV geometry (i.e. normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy), as previously defined.[10] We will also consider repeating all analyses in the subset of individuals without prevalent cardiovascular disease (coronary heart disease, TIA/stroke, or heart failure).

All analyses will be performed using STATA v11.2 (StataCorp, College Station, TX).

Limitations and challenges. Because these analyses will be essentially cross-sectional, causal relationships cannot be inferred.

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)?

MS #529 (Eigenbrodt) Distribution and associations of valvular lesions in the Jackson ARIC cohort

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

Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: A population-based study. *Lancet*. 2006;368:1005-1011.

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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