1.a. Full Title: Valvular heart disease and cardiac remodeling, damage, and overload in older adults

b. Abbreviated Title (Length 28 characters): Valve disease and cardiac damage

2. Writing Group:
   Writing group members:

Jonathan Rubin, MD, MHS; Kunihiro Matsushita, MD, PhD; Susan Cheng, MD; Ajay Kirtane MD, SM; Ron C. Hoogeveen, PhD, Christie M. Ballantyne, MD, Elizabeth Selvin, PhD, MPH; Martin B Leon, MD; Josef Coresh, MD, PhD; Scott Solomon, MD, MPH; Amil Shah, MD; others welcome.

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

First author: Jonathan Rubin, MD
Address: Columbia University Medical Center
      Department of Medicine
      Division of Cardiology
      622 West 168th Street
      PH 3 Stem Room 137
      New York, NY 10032

Phone: 443-799-5543
E-mail: jr3466@cumc.columbia.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: Kunihiro Matsushita, MD, PhD
Address: Johns Hopkins Bloomberg School of Public Health
      Welch Center for Prevention, Epidemiology, and Clinical Research
      2024 E. Monument St., Suite 2-600 (Rm 2-602), Baltimore, MD 21287
      Tel (443) 287-8766  Fax (443) 683-8358

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 States 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\(^3\).

With increasing data on the safety and durability of these less invasive strategies (compared with open surgical therapies for valvular heart disease), the therapeutic indications may be broadened to patients at earlier stages of the valvular diseases. Therefore, it is important to understand the impact of valvular diseases at early stages on cardiac structure and function. Unfortunately, most studies of patients with valvular diseases originate from patients at severe stages who are referred for medical or surgical therapy\(^4\)-\(^7\). As a result, there is limited information on the impact of milder forms of valvular disease on cardiac remodeling and function.

To date, there have been no population-based studies exploring the association of valvular disease with ventricular remodeling and biomarkers of early cardiac damage and overload. Therefore, using data from the ARIC visit 5 we will assess the relationship of valvular diseases to cardiac structure, function, and biomarkers.

5. **Main Hypothesis/Study Questions:**

Each valvular condition (aortic stenosis and regurgitation and mitral stenosis and regurgitation) will be associated with:

a) Cardiac echo measures of remodeling (described below) independently of cardiovascular risk factors

b) Subclinical chronic myocardial damage, as assessed by high sensitivity troponin T, and cardiac overload represented by NT-proBNP independently of cardiac remodeling measures

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:** Cross sectional cohort study of patients attending ARIC visit 5.

**Inclusions**

All black and white ARIC subjects with echocardiogram data during visit 5 who have data on NT-proBNP and hs-cTnT available (n \(\approx 6,000\)).

**Exclusions:**

Ethnicity other than black or white, missing echocardiogram during visit 5, missing hs-cTnT or NT-proBNP at visit 5, or missing covariates of interest.
Exposure: Presence/absence and severity of aortic stenosis, aortic regurgitation, mitral regurgitation, and mitral stenosis, will be defined according to AHA/ACC/EAE guidelines whenever possible. Exact categories will be coordinated with the project based on MP # 2089 “Contemporary Burden of Valvular Disease in the Community” led by the ARIC Echo Reading Center but we summarize the current plan below. 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.

1. Aortic stenosis severity will be quantitated by use of the peak transaortic jet velocity and the mean transaortic gradient and classified:
   a. Mild with mean gradient less than 20 mm Hg, or jet velocity between 2.6 and 3.0 m per second.
   b. Moderate with mean gradient between 20 and 39 mm Hg, or jet velocity between 3.0 and 3.9 m per second.
   c. Severe with mean gradient greater than 40 mm Hg, or jet velocity greater than 4.0 m per second.

2. Aortic regurgitation severity was qualitatively assessed and categorized into trace, mild, moderate and severe.

3. Mitral stenosis was qualitatively assessed and categorized into mild, moderate and severe. We expect few persons with mitral stenosis but are including here for completeness.

4. Mitral regurgitation severity will be quantified by color Doppler using the ratio of regurgitant jet area to the left atrial area and classified as either none, trace (≤5%), mild (5%-20%), moderate (20%-40%), or severe (>40%)

Outcome (dependent) variables:

a) Echocardiographic
   -V mass index (g/m²) = LV mass/BSA
   -LV relative wall thickness
   -LV end-diastolic diameter
   -LV posterior wall thickness (PWT)
   -interventricular septal thickness (IVST)
   -Ejection fraction
   -left atrial volume
   -left atrial volume index
   -aortic root diameter
   -systolic pulmonary artery pressure
   -peak tricuspid regurgitation velocity
   -peak RV-RA gradient
- right ventricular size
- E/A ratio

b) Biomarkers
- hs-cTnT
- NT-proBNP

Covariates
Other variables of interest will include age, sex, race, center, smoking status, body mass index, waist-hip ratio, blood pressure, hypertensive medication use, diabetes, education, triglycerides, HDL and LDL cholesterols, lipid lowering medications, and kidney function (estimated GFR from serum creatinine).

Statistical Analysis
Baseline characteristics will be compared across categories of severity of aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation, and tricuspid regurgitation.

We will use linear and logistic models to assess the association between each valvular condition (mild or greater) and outcome variables (cardiac echo parameters and biomarkers). For our echocardiographic parameters we will perform analysis as both continuous variables and categorical variables, based on clinical cutpoints, if available, or the upper quartile. For cardiac biomarkers, similarly, we will perform analysis as continuous (log-transformed) and categorical (based on clinical cutpoints) outcome variables. For, the association of each valvular lesions with NT-proBNP and hs-cTnT, we will contrast models with and without adjusting for cardiac echo parameters such as LV mass index. Similar analysis will be performed combining multiple coexisting valvular lesions.

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

Limitations
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. Also, given the cross-sectional nature of our analysis, causation 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)?

We list below proposals incorporating valvular disease. MP #  2089 “Contemporary Burden of Valvular Disease in the Community“ seems most relevant, but this proposal will mainly focus on the prevalence of valvular diseases but does not plan to comprehensively assess their contributions to cardiac remodeling, damage, and overload. Furthermore, key authors from MP 2089 are involved in this new manuscript proposal.

# 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

# 1917 Association of diastolic dysfunction with high sensitivity troponin T and NT-proBNP across left ventricular geometries in the community: A preliminary analysis from the ARIC study. Shah, A

# 1537 Echocardiographic Predictors of Incident CHF and Cardiovascular Events in African Americans. Fox, ER

# 1922 Design of a multicenter echocardiographic study to assess the relationship between cardiac structure and function and heart failure risk in free-living elderly subjects Shah, A

# 1943 Performance of two echocardiographic schema for grading diastolic dysfunction in an elderly community-based cohort – A preliminary analysis from the ARIC study. Shah, A

# 2089 Contemporary Burden of Valvular Disease in the Community. Cheng, S

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.cscu.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.

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