ARIC Manuscript Proposal # 3745

PC Reviewed: 12/8/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Valvular Heart Disease and Subsequent Progression of Chronic Kidney Disease: The Atherosclerotic Risk in Community (ARIC) Study

b. Abbreviated Title (Length 26 characters): **Valvular Heart Disease and Chronic Kidney Disease**

2. Writing Group:

Writing group members: Vedika Karandikar, Yasuyuki Honda, Junichi Ishigami, Pamela L. Lutsey, Michael Hall, Scott Solomon, Josef Coresh, Amil Shah, Kunihiro Matsushita

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

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3. Timeline: Analysis will commence when data is available. The manuscript will be submitted for review within 6 months of approval.

4. Rationale:

Valvular heart disease (VHD) affects about 2.5% of the US population.[1] The prevalence of VHD increases with age[2] and exceeds 13% among individuals aged 75 years and older.[1] VHD has recently attracted substantial attention in the medical field, given the introduction and wide availability of novel percutaneous valve replacement therapies, TAVR and MitraClip.[3,4] These treatments have been associated with improved valve hemodynamics and decreased mortality in patients at high-risk for surgical intervention.[3,5–7] This has large implications as VHD is a progressive disease which, without treatment, can lead to several complications such as heart failure and death.[8,9]

Chronic kidney disease (CKD) may also be a potential complication of VHD. Recently, several studies have demonstrated an improvement in kidney function after percutaneous valve replacement therapy for VHD (TAVR[10–13] and MitraClip[14,15]). These findings suggest an association of hemodynamic abnormalities caused by VHD with impaired kidney function.[10,15,16] However, to our knowledge, there is no literature evaluating the longitudinal CKD progression in individuals with VHD who have not undergone valve replacement therapy.

Therefore, we will primarily assess the association of VHD (e.g., aortic stenosis, aortic regurgitation, and mitral regurgitation) evaluated by echocardiography at ARIC visit 5 (2011-2013) with subsequent risk of incident CKD. In our secondary analysis, we plan to assess the cross-sectional association of VHD with the prevalence of CKD at visit 5 as well. This research has important implications in understanding the etiological contribution of VHD to CKD progression.

5. Main Hypothesis/Study Questions:

1. The presence and severity of VHD (e.g., aortic and mitral valve disease) at visit 5 will be associated with incident CKD after visit 5.
2. The presence and severity of VHD at visit 5 will be cross-sectionally associated with prevalent CKD at visit 5.

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:
Primary analysis: Prospective cohort study
Secondary analysis: Cross-sectional cohort study

Inclusions/Exclusions:
Prospective analysis:

- Inclusion
  - Black and White ARIC participants at visit 5
- Exclusion
  - Missing echocardiography measures at visit 5
  - Missing eGFR or albuminuria measurements at visit 5
  - Participants with eGFR <60 ml/min/1.73 m^2 (based on the Chronic Kidney Disease Epidemiology Collaboration equation[17]) or urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g[18] at visit 5 or previous hospitalization with CKD-related diagnosis

Cross-sectional analysis:

- Inclusion
  - Black and White ARIC participants at visit 5
- Exclusion

- Missing echocardiography measures at visit 5
- Missing eGFR or albuminuria measurements at visits 5

Exposures (independent variables):
Presence and severity of valvular heart disease:

- Aortic stenosis:
  - Mild: mean gradient less than 20 mm Hg, or jet velocity 2.6-3.0 m/s
  - Moderate: mean gradient 20-39 mm Hg, or jet velocity between 3.0-3.9 m/s
  - Severe: mean gradient greater than 40 mm Hg, or jet velocity greater than 4.0 m/s
- Aortic regurgitation: categorically assessed as trace, mild, moderate, and severe
- Mitral stenosis: qualitatively assessed as mild, moderate, and severe (given small number of cases with mitral stenosis, we do not anticipate meaningful inference but are listing for completeness)
- Mitral regurgitation: quantified by color Doppler with the ratio of regurgitant jet area to the left atria area and classified as none, trace, mild, moderate, or severe.

Outcomes (dependent variables):
Prospective analysis:

-Incident CKD will be defined as eGFR <60 mL/min/1.73m^2 or ACR of ≥ 30 mg/g at visits 6 and 7 or hospitalization with CKD-related diagnosis after visit 5

Cross-sectional analysis:

-Prevalent CKD will be defined as eGFR <60 mL/min/1.73m^2 or ACR of ≥30 mg/g or previous hospitalization with CKD-related diagnosis at visit 5

Other variables of interest and covariates at visit 5:
Age, sex, race, education level, body mass index (BMI), smoking status, alcohol intake, diabetes mellitus, blood pressure, cholesterol lowering medication use, RAAS inhibitor and other antihypertensive medication use, cholesterol, high-density lipoprotein cholesterol levels, and history of coronary heart disease and heart failure.

Statistical Analysis Plan:

1. We will compare baseline characteristics across categories of severity of aortic stenosis, aortic regurgitation, mitral stenosis, and mitral regurgitation. We will use chi-square test or analysis of variance, as appropriate, to compare characteristics across VHD categories.

2. For the cross-sectional analysis, logistic regression will be used to quantify the association of VHD (present vs. absent and severity) with prevalent CKD at visit 5. We will adjust for the covariates listed above to account for the potential confounders. Specifically, Model 1 will be crude. Model 2 will be adjusted for demographics (e.g., age, sex, and race). Model 3 will be further adjusted for other cardiovascular risk factors (smoking, alcohol, hypertension, diabetes, lipids, and history of coronary heart disease and heart failure).

3. For the prospective analysis, we will use Cox proportional hazards regression models to examine the association of VHD at visit 5 with incident CKD after visit 5 using the same models mentioned above.

4. We will perform a stratified analysis to identify potential effect modifications according to age, gender, race, and comorbidities (e.g., hypertension, diabetes, history of coronary heart disease, and heart failure).

5. Since hospitalization with CKD-related diagnosis is likely to be mainly based on kidney function (given clinical attention and availability of serum creatinine), we will repeat the analysis by focusing on eGFR (but not taking into albuminuria) for defining prevalent and incident CKD.

Limitations:
As a result of the observational nature of the study, causality cannot be determined. It is also not possible to rule out the possibility of residual confounding. This is particularly for the secondary, cross-sectional analysis. Further, study participants were older than 65 years old, and thus the findings from this project may not be generalizable to younger populations.

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)?

#3529: Junichi Ishigami, Manabu Hishida, Lena Mathews, Dalane Kitzman, Josef Coresh, Scott Solomon, Amil M. Shah, Kunihiro Matsushita. Echocardiographic parameters and subsequent risk of chronic kidney disease (CKD)

#2739: Jonathan Rubin, Kunihiro Matsushita, Susan Cheng, Ajay Kirtane, Ron C. Hoogeveen, Christie M. Ballantyne, Elizabeth Selvin, Martin Leon, Josef Coresh, Scott Solomon, Amil Shah. Valvular heart disease and cardiac remodeling, damage, and overload in older adults

#1972: Kunihiro Matsushita, Amil M. Shah, Hicham Skali, Josef Coresh, Scott D. Solomon. The association of kidney disease measures with left ventricular and atrial structure and function: The Atherosclerosis Risk in Communities (ARIC) Study

MP #3529 proposed to investigate the association of echocardiographic parameters (e.g., left ventricular function or structure) with the risk of CKD, while they did not evaluate the presence or severity of VHD. Thus, our study has a novelty of exploring VHD in the context of the association with CKD.

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. 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(9540):1005-1011. doi:10.1016/S0140-6736(06)69208-8
2. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol*. 2011:162–172. doi:10.1038/nrcardio.2010.202

3. Reinöhl J, Kaier K, Reinecke H, et al. Effect of availability of transcatheter aortic-valve replacement on clinical practice. *N Engl J Med*. 2015;373(25):2438-2447. doi:10.1056/NEJMoa1500893
4. Deuschl FG, Schofer N, Lubos E, et al. MitraClip-data analysis of contemporary literature. *J Thorac Dis*. 2015;7(9):1509–1517. doi:10.3978/j.issn.2072-1439.2015.07.38
5. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363(17):1597–1607. doi:10.1056/NEJMoa1008232
6. Glower DD, Kar S, Trento A, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: Results of the EVEREST II study. *J Am Coll Cardiol*. 2014;64(2):172-181. doi:10.1016/j.jacc.2013.12.062
7. Deeb GM, Reardon MJ, Chetcuti S, et al. 3-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol*. 2016;67(22):2565-2574. doi:10.1016/j.jacc.2016.03.506
8. *Cardiovascular Disability: Updating the Social Security Listings*.; 2010. doi:10.17226/12940
9. Maganti K, Rigolin VH, Sarano ME, Bonow RO. Valvular heart disease: Diagnosis and management. *Mayo Clin Proc*. 2010;85(5):483–500. doi:10.4065/mcp.2009.0706
10. Cubeddu RJ, Asher CR, Lowry AM, et al. Impact of Transcatheter Aortic Valve Replacement on Severity of Chronic Kidney Disease. *J Am Coll Cardiol*. 2020;76(12):1410-1421. doi:10.1016/j.jacc.2020.07.048
11. Beohar N, Doshi D, Thourani V, et al. Association of transcatheter aortic valve replacement with 30-day renal function and 1-year outcomes among patients presenting with compromised baseline renal function experience from the PARTNER 1 trial and registry. *JAMA Cardiol*. 2017;2(7):742-749. doi:10.1001/jamacardio.2017.1220
12. Nijenhuis VJ, Peper J, Vorselaars VMM, et al. Prognostic Value of Improved Kidney Function After Transcatheter Aortic Valve Implantation for Aortic Stenosis. *Am J Cardiol*. 2018;121(10):1239-1245. doi:10.1016/j.amjcard.2018.01.049
13. Najjar M, Yerebakan H, Sorabella RA, et al. Reversibility of chronic kidney disease and outcomes following aortic valve replacement. *Interact Cardiovasc Thorac Surg*. 2015;21(4):499–505. doi:10.1093/icvts/ivv196
14. Kaneko H, Neuss M, Schau T, Weissenborn J, Butter C. Interaction between renal function and percutaneous edge-to-edge mitral valve repair using MitraClip. *J Cardiol*. 2017;69(2):476-482. doi:10.1016/j.jjcc.2016.03.004
15. Wang A, Sangli C, Lim S, et al. Evaluation of renal function before and after percutaneous mitral valve repair. *Circ Cardiovasc Interv*. 2015;8(1). doi:10.1161/CIRCINTERVENTIONS.113.001349
16. Lo KB, Dayanand S, Ram P, et al. Interrelationship Between Kidney Function and Percutaneous Mitral Valve Interventions: A Comprehensive Review. *Curr Cardiol Rev*. 2018;15(2):76-82. doi:10.2174/1573403x14666181024155247
17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009. doi:10.7326/0003-4819-150-9-200905050-00006
18. KDIGO. Official Journal of the international supplements Society of nephrology KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013.