ARIC Manuscript Proposal #2241

PC Reviewed: 10/8/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of kidney disease measures with arterial stiffness: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): **Kidney & arterial properties**

2. Writing Group:

Writing group members: Kunihiro Matsushita, Hirofumi Tanaka, Shoshana Ballew, Yingying Sang, Gerardo Heiss, Josef Coresh, Others welcome

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

First author: Kunihiro Matsushita
Address: Department of Epidemiology,
Johns Hopkins Bloomberg School of Public Health,
615 N. Wolfe Street (Rm W6017), Baltimore, MD 21205
Phone: (443) 287-8766 Fax: (410) 955-8086
E-mail: kmatsush@jhsph.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:
Address:

Phone: Fax:
E-mail:

3. Timeline: Analysis will begin following proposal approval and completion of visit 5 data cleaning. A manuscript will be completed within 6 months after receiving necessary data for this proposal.

4. Rationale:

Chronic kidney disease (CKD), characterized by reduced kidney function or kidney damage, is a major global public health problem.[1, 2] CKD affects over 10% of adults in the world[3-6] and is an independent predictor of adverse outcomes.[7, 8] Cardiovascular

disease (CVD) is one of the most important adverse outcomes among individuals with CKD, as it is the leading cause of death in this population.[9] Increased CVD risk in patients with CKD is accounted for only in part by conventional risk factors,[10] and other mechanisms are yet to be elucidated.

In this context, arterial stiffness has attracted attention of clinicians and investigators as a potential mechanism linking CKD to CVD.[11] Indeed, several studies demonstrate the association of CKD with arterial stiffness.[11-16] However, most of these studies focused on either of two key kidney measures, glomerular filtration rate (GFR) and albuminuria, but not both, investigated clinically selected population (e.g., hypertension or diabetes), include a small number of participants (often n< 1000), and did not evaluate a gold standard measure of arterial stiffness, i.e., carotid-femoral pulse wave velocity (PWV). Thus, a comprehensive examination of two key kidney measures and arterial stiffness in a large sample from the general population with broad range of kidney status is needed.

PWV and ankle-brachial index (ABI) in the fifth visit of the Atherosclerosis Risk in Communities (ARIC) Study, therefore, provides an excellent opportunity to assess the associations of estimated GFR and albuminuria with arterial stiffness including the gold standard measure in a bi-ethnic community-based population with ~8000 older individuals. As the prevalence of CKD drastically increases along with age (from 4% at age 20-39 to 47% at age ≥70 years in the US),[17] the data from this cohort of older individuals are important.

5. Main Hypothesis/Study Questions:

Two key kidney disease measures are cross-sectionally associated with arterial stiffness independently of each other and conventional cardiovascular risk factors

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).

Inclusions:

- All black and white ARIC subjects with data on kidney disease measures (serum creatinine and cystatin C and albuminuria) and PWV/ABI at visit 5

Exclusions:

-Ethnicity other than black or white

-Missing data on kidney disease measures and PWV/ABI

Exposure (independent variables):

-estimated GFR (eGFR)

eGFR will be calculated using the recently proposed CKD-EPI equation[18] incorporating data of serum creatinine concentration, age, gender, and race at visit 5 and measured in ml/min/1.73 m^2. We will also evaluate the consistency of our results by using eGFR incorporating age, gender, race, serum creatinine and cystatin C.[19] Although our primary exposure will be eGFR at visit 5, using

previous ARIC visits, we will also assess the association of eGFR overtime (cumulative exposure and change) with measures of atrial stiffness.

-albuminuria

As recommended in clinical guidelines,[2] urinary albumin-to-creatinine ratio (ACR) will be used as a measure of albuminuria. As will be done for eGFR, our primary exposure will be ACR at visit 5, but we will also assess ACR overtime (from visit 4 to visit 5).

Outcome (dependent variables):

-Arterial stiffness measures

- Carotid-femoral PWV
- Brachial-ankle PWV
- Carotid artery augmentation index
- Central pulse pressure (considered to reflect aortic compliance and stroke volume)[12]
- Total systemic arterial compliance ([stroke volume]/[aortic pulse pressure])[13]
- ABI (a high ABI is considered as a marker of lower extremity arterial stiffness)[20]

Other variables of interest and covariates:

-Sociodemographics: age, race, gender, education level
-Physical information: body mass index, waist circumference, blood pressure, heart rate
-Lifestyle: smoking status, alcohol habit, and physical activity
-Comorbidities: Diabetes, hypertension, dyslipidemia, and history of CVD (coronary heart disease, stroke, and heart failure), inflammation (high-sensitivity C-reactive protein)

Statistical Analysis Plan:

The primary analysis will use linear regression models to quantify the association between kidney disease measures and arterial stiffness measures. eGFR and ACR will be treated as continuous variables with splines and categorical variables based on clinical categories (eGFR: <15, 15-29, 30-44, 45-59, 60-89, and 90+ ml/min/1.73m^2 and ACR: <30, 30-299, and 300+ mg/g) in the models. We will adjust for the covariates listed above. We will test interaction of these kidney measures on the associations with arterial stiffness parameters. We will repeat the analysis after stratifying the study sample by age, gender, race, and presence/absence of comorbidities such as obesity and diabetes. For arterial stiffness variables with clinical cutoff points (e.g., ABI ≥1.4 [or incompressible] or <0.9), we will also run logistic regression models with dichotomized dependent variables.

We will conduct a few sensitivity analyses. Firstly, to evaluate the impact of extreme values, we will exclude individuals with CKD stage 5 (eGFR <15) or ESRD at visit 5. Secondly, we will exclude individuals with history of cardiovascular disease. Finally, we will exclude participants who are taking medications with hemodynamic effects, such as renin angiotensin system inhibitors, beta-blockers, or diuretics.

Limitations:

A cross-sectional design will not allow us to evaluate causality of the associations. As with any observational study, we will not be able to rule out the possibility of residual confounding. The results may not be generalizable to younger population or ethnic groups other than whites and blacks.

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)?
There are no proposals looking at the association between CKD and measures of atrial stiffness in ARIC using visit 5 PWV/ABI data.

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. Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, Nahas ME, Jaber BL, Jadoul M, Levin A, Powe NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G. Chronic kidney disease as a global public health problem: Approaches and initiatives - a position statement from kidney disease improving global outcomes. *Kidney Int*. 2007;72:247-259
2. National Kidney Foundation. K/doqi clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1-266
3. Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, Chiang PH, Hsu CC, Sung PK, Hsu YH, Wen SF. All-cause mortality attributable to chronic kidney disease: A prospective cohort study based on 462 293 adults in taiwan. *Lancet*. 2008;371:2173-2182
4. Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, Atkins RC. Prevalence of kidney damage in australian adults: The ausdiab kidney study. *J Am Soc Nephrol*. 2003;14:S131-138
5. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, Hallan HA, Lydersen S, Holmen J. International comparison of the relationship of chronic kidney disease prevalence and esrd risk. *J Am Soc Nephrol*. 2006;17:2275-2284
6. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the united states. *JAMA*. 2007;298:2038-2047
7. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M, for the Alberta Kidney Disease N. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*. 2010;303:423-429
8. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet*. 2010;375:2073-2081
9. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the american heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation*. 2003;108:2154-2169
10. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet*. 2000;356:147-152
11. Schillaci G, Pirro M, Mannarino MR, Pucci G, Savarese G, Franklin SS, Mannarino E. Relation between renal function within the normal range and central and peripheral arterial stiffness in hypertension. *Hypertension*. 2006;48:616-621
12. Upadhyay A, Hwang SJ, Mitchell GF, Vasan RS, Vita JA, Stantchev PI, Meigs JB, Larson MG, Levy D, Benjamin EJ, Fox CS. Arterial stiffness in mild-to-moderate ckd. *J Am Soc Nephrol*. 2009;20:2044-2053

13. Hermans MM, Henry R, Dekker JM, Kooman JP, Kostense PJ, Nijpels G, Heine RJ, Stehouwer CD. Estimated glomerular filtration rate and urinary albumin excretion are independently associated with greater arterial stiffness: The hoorn study. *J Am Soc Nephrol*. 2007;18:1942-1952
14. Wang MC, Tsai WC, Chen JY, Huang JJ. Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. *Am J Kidney Dis.* 2005;45:494-501
15. Briet M, Bozec E, Laurent S, Fassot C, London GM, Jacquot C, Froissart M, Houillier P, Boutouyrie P. Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. *Kidney Int*. 2006;69:350-357
16. Madero M, Wassel CL, Peralta CA, Najjar SS, Sutton-Tyrrell K, Fried L, Canada R, Newman A, Shlipak MG, Sarnak MJ. Cystatin c associates with arterial stiffness in older adults. *J Am Soc Nephrol*. 2009;20:1086-1093
17. Hallan SI, Matsushita K, Sang Y, Mahmoodi BK, Black C, Ishani A, Kleefstra N, Naimark D, Roderick P, Tonelli M, Wetzels JF, Astor BC, Gansevoort RT, Levin A, Wen CP, Coresh J. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012;308:2349-2360
18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612
19. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS. Estimating glomerular filtration rate from serum creatinine and cystatin c. *N Engl J Med*. 2012;367:20-29
20. Ix JH, Katz R, De Boer IH, Kestenbaum BR, Allison MA, Siscovick DS, Newman AB, Sarnak MJ, Shlipak MG, Criqui MH. Association of chronic kidney disease with the spectrum of ankle brachial index the chs (cardiovascular health study). *J Am Coll Cardiol*. 2009;54:1176-1184