ARIC Manuscript Proposal #2516

PC Reviewed: 3/10/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Subclinical atherosclerosis and incident end-stage renal disease: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): **Atherosclerosis & ESRD**

2. Writing Group:

Writing group members: Yuanjie Pang, Yingying Sang, Shoshana Ballew, Morgan Grams, Gerardo Heiss, Josef Coresh, Kunihiro Matsushita

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

First author: Yuanjie Pang
Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, Baltimore, MD 21205
Phone: (410) 736-0522 Fax:
E-mail: ypang3@jhu.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
Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, Baltimore, MD 21205
Phone: (443) 287-8766 Fax: (443) 683-8358
E-mail: kmatsush@jhsph.edu

3. Timeline: Analysis will begin following proposal approval and, a manuscript will be completed within 6 months.

4. Rationale:

Atherosclerosis is characterized by arterial wall thickening due to the deposition of plaque consisting of lipoprotein particles, macrophages, and smooth muscle cells.[1,2] Representative risk factors for atherosclerosis include age, dyslipidemia, hypertension, cigarette smoking, and hyperglycemia.[3-9] Atherosclerosis is a leading cause of coronary

heart disease (CHD) and stroke. Although the incidence of atherosclerotic cardiovascular disease has been decreasing over several decades, of note, it is still a leading cause of death in the United States.[10,11]

Atherosclerosis can also impact kidney function through a few mechanisms. Atherosclerotic renal artery stenosis is a representative example and may lead to kidney dysfunction mainly through hypertension due to activated renin angiotensin system.[12] Indeed, as much as 14% of end-stage renal disease (ESRD) is attributable to chronic ischemic nephropathy from renal artery stenosis.[13] Moreover, some studies suggest the link between atherosclerosis of intrarenal vasculature and glomerulosclerosis.[14] On the other hand, it is also possible that atherosclerosis and kidney disease merely share common pathogenic mechanisms or risk factors such as diabetes and hypertension.[14]

Elsayed et al. have reported that kidney function declines faster among persons with atherosclerotic disease (CHD, stroke, and peripheral artery disease) than those without.[15] However, treatment or clinical examinations in those with atherosclerotic disease (e.g., iodinated contrast agent) may have confounded this association. In this connection, measures of subclinical atherosclerosis (e.g., carotid intima-media thickness [IMT] and ankle-brachial index [ABI]) would be of value, and indeed several studies have observed those measures predating kidney disease progression.[16-24] However, most of them dealt with selected populations of white race[16-18] or older adults[19,20], leaving uncertainty regarding their generalizability. Also, of those studies, only one study investigated multiple measures of subclinical atherosclerosis[18] (ABI and carotid IMT), and thus it is not clear whether the magnitude of associations, if any, varies across subclinical atherosclerosis measures. Most importantly, none of previous studies have evaluated ESRD, the most severe form of kidney disease with disproportionate high medical expenditure, as a kidney outcome.[16-23]

Thus, we will comprehensively evaluate several measures of subclinical atherosclerosis such as carotid IMT, carotid plaque, ABI, and popliteal IMT and their relationships to incident ESRD over 20 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study, a large community-based bi-ethnic cohort of middle-aged population.

5. Main Hypothesis/Study Questions:

Subclinical atherosclerosis is prospectively associated with incident end-stage renal disease independently of conventional kidney disease 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 white and black ARIC participants with data on measures of subclinical atherosclerosis (carotid IMT, carotid plaque, popliteal IMT and ABI) at visit of interest and incident ESRD during follow-up

Exclusions:
- Race other than white or black
- Missing data on subclinical atherosclerosis at baseline and incident ESRD during follow-up
- Estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m^2 at visit of interest

Exposures (independent variables):

We will use data at visit 1 with most rich data on subclinical atherosclerosis measures and longest follow-up for ESRD for primary analysis but will repeat the analysis for other visits, whenever possible, as secondary analysis.

- Carotid IMT (available at visits 1 through 4) was measured from the blood-intimal to the medial-adventitial interface, and thus represent the sum of the intimal and medial thicknesses.[25] Carotid arteries were examined bilaterally at three sites: the level of the common carotid (1cm proximal to the dilatation of the carotid bulb), the carotid bifurcation (1cm proximal to the flow divider), and the internal carotid artery (1cm distal to the flow divider). Ultrasound readers record the presence of atherosclerotic plaque, without reference to plaque morphology.[26,27] Carotid ultrasound data are available at visit 1 through 4, and thus will allow us to adjust for albumin-creatinine ratio (ACR) at visit 4 as sensitivity analysis
- Carotid plaque (available at visits 1 through 4): A dichotomous variable of presence or absence of plaque will be used for the analysis.
- The ABI (available at visit 1 in the entire study population and at visits 3 and 4 in subsample) is the ratio of systolic blood pressure (SBP) at the ankle to SBP at the brachial artery. Ankle and brachial SBP measurements were ascertained using the Dinamap 1846 SX (Critixon, Tampa, Fla).[28] Ankle blood pressure was measured at the posterior tibial artery in one leg. Ankle SBP is defined as the fourth SBP readings or to be the third, second, or first non-missing readings in this order if the fourth SBP readings are missing. Brachial SBP is defined as the first arm SBP or the second SBP if the first SBP readings are missing.The ABI was computed by dividing the ankle SBP by brachial SBP.[29]
- Popliteal arterial IMT (available only at visit 1) was measured in a single leg (the side randomly determined for ABI measurement) using the method described above for carotid IMT.

Outcome (dependent variables):

Incident ESRD was defined as initiation of dialysis therapy, transplantation, or death due to kidney disease.[30] Cases with dialysis therapy and transplantation were identified by linkage to the US Renal Data System (USRDS), which captures information about all Americans who receive renal replacement therapy or are awaiting kidney transplantation.[31] Participants who were free of ESRD by December 31, 2010, were administratively censored.

Other variables of interest and covariates:
-Socio-demographics: age, sex, race
-Lifestyle factors: smoking status, alcohol intake

-Physical measurements: body mass index (BMI), blood pressure
-Comorbidities: dyslipidemia, hypertension, diabetes, and history and incidence of cardiovascular disease (CVD) (CHD, stroke, and heart failure), kidney function (eGFR) and damage (ACR [only at visit 4])

Statistical Analysis Plan:

As described above, we will use visit 1 data as baseline in primary analysis. Whenever possible, we will repeat the analysis with other visits with emphasis on visit 4, which will allow us to account for ACR, a potent risk factor for ESRD.[32]

Carotid IMT, popliteal IMT, and ABI will be modeled using both quartiles and 1-SD increment in each measure. ABI will also be evaluated based on following six categories (<0.9, 0.9-1.0, 1.0-1.1, 1.1-1.2, 1.2-1.3, >1.3) according to clinical threshold and literature.[33,34] Baseline characteristics will be summarized according to the quartiles or clinical categories of each subclinical measure, and differences across the quartiles or clinical categories will be assessed by chi-square test and analysis of variance, as appropriate.

To visualize the potentially nonlinear association between each subclinical measure and ESRD, incidence rate of ESRD adjusted for age, sex, and race will be evaluated using a Poisson regression model with linear splines (3 knots corresponding to cut-offs of the quartiles of carotid IMT and popliteal IMT and 5 knots to cut-offs of the clinical categories of ABI).

We will first evaluate the correlations among subclinical measures and eGFR. We will then quantify the association of each subclinical measure with incident ESRD using Cox proportional hazards models. We will use 5 statistical models with progressive adjustment. Model 1 is unadjusted. In model 2, we will adjust for age, sex, and race. In model 3, we will further adjust for SBP, antihypertensive medication, smoking status, alcohol intake, BMI, total and high-density lipoprotein cholesterol levels, diabetes, and history of CVD. Model 4 additionally adjust for eGFR (and ACR for visit 4 analysis). Model 5 will further include the other three subclinical measures (e.g., adjusting for carotid plaque, popliteal IMT, and ABI for the analysis of carotid IMT).

We will conduct several sensitivity analyses. First, we will examine the association in subgroups defined by age (<55 vs ≥55 years), sex, race, presence/absence of diabetes, hypertension, obesity, reduced eGFR (<60 vs ≥60 mL/min/1.73 m^2), high albuminuria (ACR<30 vs ≥30 mg/g), and history of CVD. The likelihood ratio test will be used to test interactions. Second, we will conduct competing-risk analysis with death as a competing endpoint of ESRD. Third, we will include incident CHD and heart failure events during follow-up as time-varying covariates. All statistical analyses and graphical displays will be performed using Stata version 13.0 (StataCorp LP, College Station, Texas).

Limitations:

Popliteal IMT and ABI were both measured in single leg. Some key measures are only available at limited visits (e.g., popliteal IMT only at visit 1, ABI at visit 3 and 4 only in subsample, and ACR only at visit 4). We may have limited number of ESRD

events in participants of certain quartile/category of subclinical measures, and thus may not have enough power in certain strata in subgroup analysis. In addition, this study may not be exempt from residual confounding.

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 proposal looking at measures of sublicnial atherosclerosis and their associations with ESRD risk. However, a few proposals listed below have some conceptual similarity.
-ARIC manuscript proposal #504 "Does a low ankle-brachial index predict the development of renal insufficiency?" looks at low ABI and the development of renal insufficiency between visits 1 and 4.
-ARIC manuscript proposal #1058 "Kidney Function and Risk of Peripheral Arterial Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study" evaluates CKD as a predictor of PAD (opposite directionality from our current proposal).
- ARIC manuscript proposal #2241 "The association of kidney disease measures with arterial stiffness: The Atherosclerosis Risk in Communities (ARIC) Study" investigates the association between CKD and measures of atrial stiffness in ARIC using visit 5 data. High ABI is included as a marker of arterial stiffness.

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. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002:105:1135-1143.
2. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation* 1995:*92*:1355-1374.
3. McGill HC Jr, McMahan CA, Malcom GT, et al. Relation of glycohemoglobin and adiposity to atherosclerosis in youth.*Arterioscler Thromb Vasc Biol* 1995;15:431-440.
4. McGill HC Jr, McMahan CA, Malcom GT, et al. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women.*Arterioscler Thromb Vasc Biol* 1997;17:95-106.
5. Stamler J, Daviglus ML, Garside DB, et al. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA* 2000;284:311-318.
6. Bild DE, Folsom AR, Lowe LP, et al. Prevalence and correlates of coronary calcification in black and white young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Arterioscler Thromb Vasc Biol* 2001;21:852-857.
7. McCarron P, Smith GD, Okasha M, McEwen J. Blood pressure in young adulthood and mortality from cardiovascular disease. *Lancet* 2000;355:1430-1431.
8. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *New England Journal of Medicine* 2004;*351*:2599-2610.
9. Hackam DG, Sonia SA. Emerging risk factors for atherosclerotic vascular disease: a critical review of the evidence. *JAMA* 2003:290:932-940.
10. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease.*J Am Med Assoc* 2003;290:898 -904.
11. Jemal A, Ward E, Hao Y, et al. Trends in the leading causes of death in the United States, 1970-2002. *JAMA* 2005;294:1255-1259.

12. Garovic VD, Textor SC.Renovascular hypertension and ischemic nephropathy.*Circulation* 2005;112: 1362-1374.
13. Preston RA, Epstein M.Ischemic renal disease: an emerging cause of chronic renal failure and end-stage renal disease. *J Hypertens* 1997;15:1365-1377.
14. Kasiske BL. Relationship between vascular disease and age-associated changes in the human kidney. *Kidney Int* 1987;31:1153-1159.
15. Elsayed EF, Tighiouart H, Griffith J, et al. Cardiovascular disease and subsequent kidney disease. *Arch Intern Med* 2007;167:1130-1136.
16. Rahman M, Xie D, Feldman HI, et al. Association Between Chronic Kidney Disease Progression and Cardiovascular Disease: Results from the CRIC Study. *Am J Nephrol* 2014;40:399-407.
17. Chonchol M, Gnahn H, Sander D. Impact of subclinical carotid atherosclerosis on incident chronic kidney disease in the elderly. *Nephrol Dial Transplant* 2008;23: 2593-2598.
18. Shlipak MG, Katz R, Kestenbaum B,et al. Clinical and subclinical cardiovascular disease and kidney function decline in the elderly. *Atherosclerosis* 2009;204:298-303.
19. Foster MC, Ghuman N, Hwang SJ, et al. Low ankle-brachial index and the development of rapid estimated GFR decline and CKD. *Am J Kidney Dis* 2013;61:204-210.
20. Kshirsagar AV, Bang H, Bomback AS,et al. A simple algorithm to predict incident kidney disease. *Arch Intern Med* 2008;168:2466-2473.
21. O'Hare AM, Rudolph AR, Bacchetti P. Low ankle-brachial index associated with rise in creatinine level over time: results from the atherosclerosis risk in communities study. *Arch Intern Med* 2005;165:1481-1485.
22. Yu Z, Schneck M, Jacobs Jr DR, et al. Association of carotid intima-media thickness with progression of urine albumin-creatinine ratios in The Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis* 2011;57:62-70.
23. Shimizu M, Furusyo N, Mitsumoto F, et al. Subclinical carotid atherosclerosis and triglycerides predict the incidence of chronic kidney disease in the Japanese general population: Results from the Kyushu and Okinawa Population Study (KOPS). *Atherosclerosis* 2015;238:207-212.
24. Mittalhenkle A, Stehman-Breen CO, Shlipak MG, et al. Cardiovascular risk factors and incident acute renal failure in older adults: the cardiovascular health study. *Clin J Am Soc Nephrol* 2008;3:450-456.
25. Pignoli P,Tremoli E,Poli A,etal. Intimal plus medial thickness of arterial wall: a direct measurement with ultrasound imaging. *Circulation* 1986; 74:1399-1406.
26. National Heart,Lung,and Blood Institute.Atherosclerosis Risk in Communities (ARIC) Study. Operations manual,no.6A: ultrasound scanning methods.Version1.0.ChapelHill,NC: ARIC Coordinating Center,School of Public Health,University of North Carolina,1987.
27. National Heart,Lung,and Blood Institute.Atherosclerosis Risk in Communities (ARIC) Study Operations manual, no.6B: ultrasound reading methods.Version1.0.ChapelHill,NC:ARIC Coordinating Center,School of Public Health,University of North Carolina,1987.
28. National Heart, Lung, and Blood Institute. Atherosclerosis Risk in Communities (ARIC) Study. Manuals of operation. 12 vols. Chapel Hill NC: ARIC Coordinating Center, School of Public Health, University of North Carolina, 1987.
29. Mundt KA, Chambless LE, Burnham CB, et al. Measuring ankle systolic blood pressure: validation of the Dinamap 1846 SX. *Angiology* 1992; 43:555-566.
30. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD Study equation for estimated glomerular filtration rate.*JAMA*2012;307(18):1941-1951.
31. van Walraven C, Manuel DG, Knoll G. Survival trends in ESRD patients compared with the general population in the United States.*Am J Kidney Dis* 2014;63(3):491-499.
32. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA* 2011;305:1553-1559.
33. Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;2:197.
34. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for

Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines. *Circulation* 2006;113:463-654.