

ARIC Manuscript Proposal # 3628

PC Reviewed: 5/12/20
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Estimated glomerular filtration and albuminuria and calcification of coronary arteries, aorta, and cardiac valves in older adults

b. Abbreviated Title (Length 26 characters): Kidney measures and CAC

2. Writing Group:

Writing group members: Yejin Mok, Frances Wang, Shoshana H. Ballew, Steve Menez, Kenneth R Butler, Lynne Wagenknecht, Aaron Folsom, Josef Coresh, Michael Blaha, Kunihiro Matsushita

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

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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).

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3. Timeline: Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Chronic kidney disease (CKD) increases the risk of cardiovascular disease (CVD) (1,2). Although there are several pathophysiological mechanisms linking CKD to CVD, vascular calcification is considered as a pivotal contributor since the kidney plays a vital role in calcium-

phosphate metabolism (3). Indeed, several studies have shown a higher prevalence of coronary artery calcification (CAC) in patients with end-stage renal disease (4,5). However, conflicting results have been reported regarding the association of mild to moderate CKD with CAC (6-18). For example, the Multi-Ethnic Study of Atherosclerosis (MESA) reported that low estimated glomerular filtration (eGFR) was not associated with CAC after adjustment for demographic and clinical factors.(6) The Framingham Offspring Study showed that neither eGFR nor albuminuria was associated with CAC.(13)

No or weak associations between CKD and CAC may sound counterintuitive but actually may be plausible. Specifically, there are two types of vascular calcification, intimal calcification and medial calcification. CKD is known to accelerate medial calcification while CAC is predominantly intimal calcification.

To better understand this potentially complex association of mild to moderate CKD and CAC, we will comprehensively evaluate the association of two key CKD measures, eGFR and urine albumin-to-creatinine ratio (ACR) with CAC in the ARIC Study. ARIC has one of the largest existing datasets of CAC measurements in individuals aged 75 years and older, and provides unique opportunities to study this association. Also, we will be able to assess the association of CKD with extra-coronary artery calcification (ECC) like aortic valve calcification.

5. Main Hypothesis/Study Questions:

- Both CKD measures, lower eGFR and higher ACR, will be independently associated with greater CAC.
- Both CKD measures will be independently associated with prevalence of ECC (i.e., ascending aorta, aortic valve ring, aortic valve calcification, descending aorta, and mitral valve calcification).

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: Prospective study

- We will quantify the association of low eGFR and high ACR at a middle (visits 1-4) and older (visit 5 or 6) age with CAC at the age of 75 years or older. Since we would like to have at least a minimal lag time between CKD measurements and CAC/ECC assessment, we are not planning to use CKD data at visit 7 in this study.

Inclusion:

- All ARIC participants who have eGFR, ACR, and other necessary covariates at baseline will be included in the analyses.

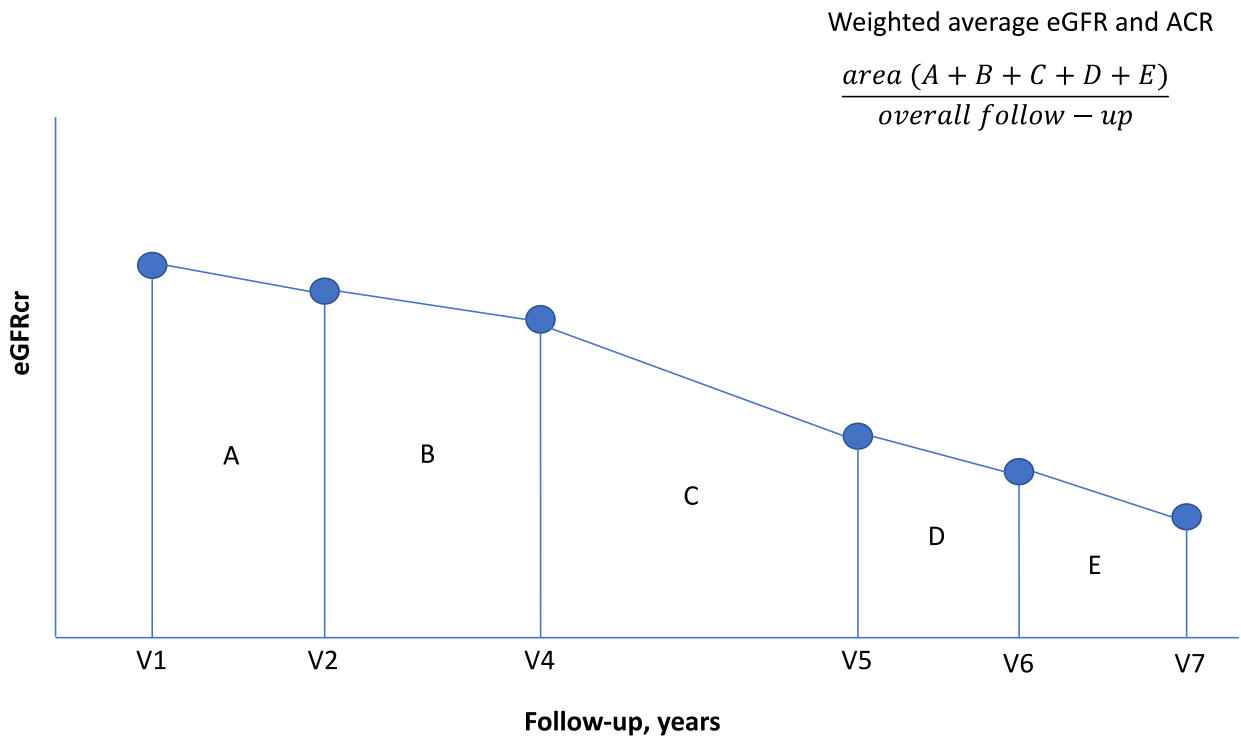
Exclusion:

- Individuals with prevalent coronary heart disease at visit 7 (study design of ARIC CAC ancillary)
- Missing CAC data
- Missing data on CKD measures and covariates of interest
- Ethnicity other than black and white

Exposures:

- **CKD measures (eGFR and ACR)**
 - eGFR calculated by CKD Epidemiology Collaboration (CKD-EPI) equation
 - We will primarily use serum creatinine+cystatin C based eGFR since this is the best available equation. Nonetheless, we will secondarily use eGFR based on serum creatinine or cystatin C.
 - ACR as a measure of albuminuria as recommended in the Kidney Disease Improving Global Outcomes (KDIGO) CKD guidelines (19)
 - Since CKD usually progresses over time, CKD data at visit 5 are likely to reasonably reflect the exposure in the past and thus we will use this visit for primary analysis. Nonetheless, we will also use the cumulative eGFR and ACR (weighted average eGFR and ACR) during ARIC follow-up. For example, we will calculate each trapezoid between each visit (area A will be calculated based on levels of CKD measures at visit 1 and 2, time differences between visit 2 and visit 1), calculate sum of each trapezoid (A-E), then divide sum of each trapezoid by overall follow-up time. We will also explore “CKD-years” (i.e., years with CKD status) as an exposure. To best estimate kidney function, we will primarily use eGFR based on both serum creatinine and cystatin C but will also explore eGFR based on either of these filtration markers.

Figure. Weighted average eGFR and ACR



- **Covariates of interest:** socio-demographic characteristics (age, race, gender, education), alcohol intake, smoking status, body mass index, history of stroke, history of heart failure, hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, reported history of hypertension, or use of antihypertensive medication), use

of anti-hypertensive medications, diabetes (fasting blood glucose ≥ 126 mg/dl, non-fasting glucose ≥ 200 mg/dl, reported history of diabetes, or use of diabetes medication), use of anti-diabetes medications, lipid parameters (Total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride), lipid-lowering therapy, and bone-mineral metabolism markers (e.g., Ca, P, FGF23).

Outcomes:

- **CAC and ECC**

- CAC measured by non-contrast CTs were calculated using the Angoston method. CAC will be modeled as binary outcome (e.g., >0 vs. 0 , >100 vs. ≤ 100 , >500 vs. ≤ 500 , >1000 vs. ≤ 1000 , and $>\text{top } 25^{\text{th}}$ vs. $\leq\text{top } 25^{\text{th}}$) and continuous outcome ($\ln[\text{CAC}+1]$) to include participants with $\text{CAC}=0$.
- ECC includes calcification at five sites: aortic valve, aortic valve ring, mitral valve, ascending aorta, and descending aorta. This will be also modeled as binary outcome and continuous outcome.

Statistical Analysis:

1. eGFR will be categorized as <30 , 30-44, 45-50, 60-80, and ≥ 90 ml/min/1.73m² and ACR will be categorized <10 , 10-29, 30-299 and ≥ 300 mg/g (19).
2. We will summarize baseline characteristics by categories of eGFR and ACR. When we use the weighted average eGFR and ACR, we will summarize the weighted average values for continuous variables and duration of exposures for categorical variables (e.g., medication uses, hypertension, diabetes, and smoking) by categories of the weighted average eGFR and ACR.
3. Subsequently, we will quantify the association of eGFR and ACR with CAC (binary and continuous variables) using logistic regression models. Those models will adjust for covariates listed above as well as each of CKD measures (ACR will be accounted for in the analysis for eGFR and vice versa).
4. We also evaluate whether CKD measures slope is associated with CAC and calcification of vascular beds other than coronary artery. We will use linear mixed models with random intercept and random slope for each individual to estimate slope.
5. To compare the contribution of eGFR and ACR to calcification in subgroups, we will perform subgroup analysis according to age, gender and race and clinical conditions (diabetes, hypertension, and history of stroke or heart failure).
6. To account for attrition, we will implement inverse probability attrition weighting.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ___ Yes ___X___ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ___ Yes ___ No

(The 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 No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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.csc.c.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

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)?

#1246: Carotid Artery Calcification in Diabetes and the Influence of Renal Dysfunction

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes ____ 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 <https://sites.csc.c.unc.edu/aric/approved-ancillary-studies>

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.csc.c.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. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
2. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073-81.

3. Viegas C, Araujo N, Marreiros C, Simes D. The interplay between mineral metabolism, vascular calcification and inflammation in Chronic Kidney Disease (CKD): challenging old concepts with new facts. *Aging (Albany NY)* 2019;11:4274-4299.
4. Goodman WG, Goldin J, Kuizon BD et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;342:1478-83.
5. Raggi P, Boulay A, Chasan-Taber S et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002;39:695-701.
6. Ix JH, Katz R, Kestenbaum B et al. Association of mild to moderate kidney dysfunction and coronary calcification. *J Am Soc Nephrol* 2008;19:579-85.
7. Fox CS, Larson MG, Keyes MJ et al. Kidney function is inversely associated with coronary artery calcification in men and women free of cardiovascular disease: the Framingham Heart Study. *Kidney Int* 2004;66:2017-21.
8. Tuttle KR, Short RA. Longitudinal relationships among coronary artery calcification, serum phosphorus, and kidney function. *Clin J Am Soc Nephrol* 2009;4:1968-73.
9. Kramer H, Jacobs DR, Jr., Bild D et al. Urine albumin excretion and subclinical cardiovascular disease. The Multi-Ethnic Study of Atherosclerosis. *Hypertension* 2005;46:38-43.
10. Kronmal RA, McClelland RL, Detrano R et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2007;115:2722-30.
11. DeFilippis AP, Kramer HJ, Katz R et al. Association between coronary artery calcification progression and microalbuminuria: the MESA study. *JACC Cardiovasc Imaging* 2010;3:595-604.
12. Kramer H, Toto R, Peshock R, Cooper R, Victor R. Association between chronic kidney disease and coronary artery calcification: the Dallas Heart Study. *J Am Soc Nephrol* 2005;16:507-13.
13. Parikh NI, Hwang SJ, Larson MG et al. Indexes of kidney function and coronary artery and abdominal aortic calcium (from the Framingham Offspring Study). *Am J Cardiol* 2008;102:440-3.
14. Cho I, Min HS, Chun EJ et al. Coronary atherosclerosis detected by coronary CT angiography in asymptomatic subjects with early chronic kidney disease. *Atherosclerosis* 2010;208:406-11.
15. Kestenbaum BR, Adeney KL, de Boer IH, Ix JH, Shlipak MG, Siscovick DS. Incidence and progression of coronary calcification in chronic kidney disease: the Multi-Ethnic Study of Atherosclerosis. *Kidney Int* 2009;76:991-8.
16. Suh-Chiou C, Moyses RM, Bittencourt MS, Bensenor IM, Lotufo PA. Chronic kidney disease and coronary artery calcification in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Clin Cardiol* 2017;40:1309-1315.
17. Budoff MJ, Rader DJ, Reilly MP et al. Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) Study. *Am J Kidney Dis* 2011;58:519-26.
18. Hyun YY, Kim H, Oh KH et al. eGFR and coronary artery calcification in chronic kidney disease. *Eur J Clin Invest* 2019:e13101.
19. *Kidney Disease: Improving Global O. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.* New York, NY: Nature Publ. Group, 2013.