

ARIC Manuscript Proposal # 1873

PC Reviewed: 12/13/11
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Combined association of Cystatin C-based and Creatinine-based estimated Glomerular filtration rate (eGFR) with Mortality, Cardiovascular and Renal Outcomes

b. Abbreviated Title (Length 26 characters): eGFR, CV and Renal outcomes

2. Writing Group:

Writing group members: Salman Waheed (lead), Brad C Astor, Kunihiro Matsushita and Josef Coresh

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

First author: Salman Waheed
Address: Johns Hopkins University
2024 E. Monument Street, Ste. 2-600
Baltimore, MD 21205

Phone: 410-955-0495 Fax: 410-955-0476
E-mail: swaheed1@jhmi.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: **Josef Coresh**
Address: Johns Hopkins University
2024 E. Monument Street, Ste. 2-600
Baltimore, MD 21205

Phone: 410-955-0495 Fax: 410-955-0476
E-mail: coresh@jhu.edu

3. Timeline: Manuscript preparation will begin soon after we get the approval

4. Rationale:

Chronic kidney disease affects an estimated 19 million people in the United States [1]. It is defined by either the presence of reduced glomerular filtration rate (GFR) or kidney damage evidenced by the presence of protein in the urine (albuminuria). Since it is expensive and inconvenient to directly measure GFR using radioactive agents, reliance is mainly on markers that estimate GFR (eGFR). Creatinine is the most widely used measure of kidney filtration function, both in clinical practice as well in research studies, and is independently associated with mortality, cardiovascular (CV) and renal outcomes [2]. However there are several non-GFR determinants of creatinine, such as muscle mass and diet that bias the GFR estimates resulting in misclassification of risk categories. The association between eGFR by creatinine (eGFR_{cr}) and mortality is not linear but U-shaped [3]. One explanation for this U-shaped association is negative confounding of creatinine by muscle mass. This happens because sicker individuals are more likely to have decreased muscle mass and therefore lower creatinine production, resulting in overestimation of their GFR.

Cystatin C is an alternative marker of kidney function, and eGFR using cystatin C (eGFR_{cys}) has a similar correlation with measured GFR as eGFR_{cr}. It is also less sensitive to changes in muscle mass as compared to creatinine. Studies have shown a stronger and more linear association between eGFR_{cys} and mortality as well as CV outcomes compared to eGFR_{cr}, making it a more desirable marker to predict future risk [4-11]. Data from NHANES show that eGFR_{cys} has the strongest association with mortality and CV disease compared to eGFR_{cr} or using both creatinine and cystatin C based equations [3].

Recently there has been a substantial interest to investigate the association of multiple kidney markers with the risk of clinical outcomes. A recent large study used eGFR_{cr}, eGFR_{cys} and albuminuria to risk stratify individuals, and found that using the triple marker approach improves risk classification for both mortality and end-stage renal disease (ESRD) compared to one or two of these markers [12]. More research is needed to investigate the utility of multiple kidney markers; in particular, it is very important to investigate further as to which group of individuals would most likely to benefit from using a triple marker approach. It is also important to extend this to additional outcomes in particular, cardiovascular outcomes, which constitute a major proportion of morbidity and mortality in the CKD population.

5. Main Hypothesis/Study Questions:

We hypothesize that both eGFR_{cys} and eGFR_{cr} are independently associated with mortality, CV and renal outcomes. Combining the two markers of GFR (eGFR_{cys} and eGFR_{cr}), where both markers are abnormal (concordant classification), will be more strongly associated with these outcomes than either of these two measures independently. We also hypothesize that GFR estimation by cystatin C will improve classification of individuals into appropriate risk categories compared to eGFR_{cr}. We further hypothesize that in those individuals with eGFR_{cr} < 60 ml/min/1.73 m², the association with outcomes will be weaker when the other two markers are normal (eGFR_{cys} > 60 and albumin:

creatinine ratio (ACR) <30 mg/g) compared to when one or both the other markers are also in the CKD range.

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).

We plan to use ARIC visit 4 as the baseline visit, as this is the only visit with cystatin C data on all participants. We will follow the participants prospectively until December 31st, 2008 for all-cause mortality, coronary heart disease, heart failure, stroke, acute kidney injury and ESRD. We will only include incident events. We will also exclude those with missing data on any of the key variables as we assume missing data mechanism is likely missing completely at random, and therefore, would not bias our results. However, we will compare baseline characteristics of those with missing data to those who are included in our study to identify any non random patterns.

We will divide the cohort into five eGFR categories (eGFR <30, 30-59, 60-89, 90-104 (Reference), and ≥ 105), and make a 5 X 5 table with 25 combined categories of eGFR_{cys} and eGFR_{cr}. We will only analyze those cells with a sample size of at least 25 or greater. We will also further stratify by ACR and study the association of these three markers with outcomes.

We will develop multiple regression models, first adjusting only for demographics, with subsequent models also adjusting for established CVD risk factors, such as history of CVD, diabetes, hypertension, smoking, hyperlipidemia, body mass index, albuminuria, and high-sensitive C-reactive protein. We will also investigate the proportion of individuals who are reclassified into more appropriate risk categories and determine the net reclassification index. We also plan to do sub-group analyses by age (<65 years versus ≥ 65 years), race (blacks versus whites) and gender.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes
 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
 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.csc.unc.edu/ARIC/search.php>

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)?

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 at <http://www.csc.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.csc.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. Coresh, J., et al., Prevalence of chronic kidney disease in the United States. *JAMA*, 2007. **298**(17): p. 2038-47.
2. Matsushita, K., 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**(9731): p. 2073-81.
3. Astor, B.C., et al., Method of glomerular filtration rate estimation affects prediction of mortality risk. *J Am Soc Nephrol*, 2009. **20**(10): p. 2214-22.
4. O'Hare, A.M., et al., Cystatin C and incident peripheral arterial disease events in the elderly: results from the Cardiovascular Health Study. *Arch Intern Med*, 2005. **165**(22): p. 2666-70.
5. Peralta, C.A., et al., Cystatin C identifies chronic kidney disease patients at higher risk for complications. *J Am Soc Nephrol*, 2011. **22**(1): p. 147-55.
6. Sarnak, M.J., et al., Cystatin C concentration as a risk factor for heart failure in older adults. *Ann Intern Med*, 2005. **142**(7): p. 497-505.
7. Seliger, S.L., et al., Cystatin C and subclinical brain infarction. *J Am Soc Nephrol*, 2005. **16**(12): p. 3721-7.
8. Shlipak, M.G., et al., Cystatin-C and mortality in elderly persons with heart failure. *J Am Coll Cardiol*, 2005. **45**(2): p. 268-71.
9. Shlipak, M.G., et al., Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med*, 2006. **145**(4): p. 237-46.
10. Shlipak, M.G., et al., Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med*, 2005. **352**(20): p. 2049-60.
11. Shlipak, M.G., et al., Cystatin C and mortality risk in the elderly: the health, aging, and body composition study. *J Am Soc Nephrol*, 2006. **17**(1): p. 254-61.
12. Peralta, C.A., et al., Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA*, 2011. **305**(15): p. 1545-52.