ARIC Manuscript Proposal #3992

PC Reviewed: 1/11/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Risk factors for and adverse outcomes associated with discrepancies between eGFRcystatin and eGFRcreatinine

b. Abbreviated Title (Length 26 characters): eGFRcys and eGFRcr difference

2. Writing Group:

Writing group members: Danielle K. Farrington, Morgan E. Grams, Josef Coresh, Aditya Surapaneni, Kunihiro Matsushita, Jesse Seegmiller, others welcome (order TBD).

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

First author: Danielle Kacie Farrington, MD
Address: 1830 E. Monument St. / 4th Floor / Suite 416
Baltimore, MD 21287
Phone: 410-955-5268 Fax: 410-367-2258
E-mail: dfarrin1@jh.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: Morgan Erika Grams, MD, PhD
Address: 2024 E. Monument St, 2-638
Phone: 443-287-1827 Fax:
E-mail: mgrams2@jhmi.edu

3. Timeline: We will begin analyses once the manuscript proposal has been approved. We anticipate that the manuscript will be written and submitted to the ARIC Publications Committee within one year of the manuscript proposal being approved.

4. Rationale: In September 2021 the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases strongly recommended the increased use of serum cystatin C measurement in clinical care, with calculation of CKD-EPI eGFRcystatin[1,2]. Traditionally, CKD-EPI eGFRcreatinine, as calculated using the Chronic Kidney Disease Epidemiology Collaboration equations, was the preferred method of eGFR assessment[3]. However, there are known issues with non-GFR determinants of serum creatinine such as renal tubular creatinine secretion and variations in creatinine production that render eGFRcreatinine less accurate[4,5]. Cystatin C, an endogenous low-molecular weight protein, is filtered at the glomerulus and not reabsorbed[4]. Serum cystatin C is less influenced by non-GFR determinants compared to serum creatinine[5.] It is becoming more readily available and less costly, allowing for increased

assessment of eGFRcystatin[5]. eGFRcystatin is particularly helpful in situations with factors affecting serum creatinine irrespective of GFR, such as extremes of muscle mass, severe chronic illness, and advanced age[5].

While eGFRcystatin and eGFRcreatinine both accurately predict adverse outcomes[6], their values can be discrepant, creating clinical uncertainty. With the now widespread use of serum cystatin C assays, it is unknown how often large differences in eGFRcystatin and eGFRcreatinine are occurring, and what the clinical implications are. Our proposed study intends to quantify the proportion of the population having a large difference between eGFRcystatin and eGFR creatinine, and to trend the persistence of this difference over time. We also plan to evaluate both the risk factors for, and adverse outcomes associated with this discrepancy.

5. Main Hypothesis/Study Questions:

We hypothesize a large difference between eGFRcystatin and eGFRcreatinine to be associated with older age, more comorbidities, weight loss and female sex. We predict a large discrepancy between eGFRcystatin and eGFRcreatinine to be associated with the development of adverse outcomes including mortality, fractures, end-stage kidney disease, acute kidney injury, heart failure and gout.

Aims:

1. To quantify the proportion of the population having substantially lower eGFRcystatin than eGFRcreatinine.
2. To evaluate risk factors for a large difference between eGFRcystatin and eGFRcreatinine.
3. To evaluate the persistence of a large difference between eGFRcystatin and eGFRcreatinine over time.
4. To evaluate the cross-sectional association of a large difference between eGFRcystatin and eGFRcreatinine with continuous hemoglobin, phosphate, FGF-23, PTH and uric acid levels.
5. To evaluate the association of a large difference between eGFRcystatin and eGFRcreatinine with the development of adverse outcomes including mortality, fracture, ESKD, AKI, heart failure and gout.

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: We will conduct analyses of the ARIC cohort, treating visit 2 as the baseline visit for longitudinal outcomes, through 2019. For cross-sectional associations and evaluation of persistence over time, we will use all visits with available creatinine and cystatin (visit 2-6).

Study Population: The study population will consist of all ARIC participants with serum creatinine and cystatin C data from visit 2 and follow-up for outcomes for the longitudinal

analysis, and all ARIC participants with creatinine and cystatin C data at any visit for the cross-sectional analyses.

Exposure: A difference between eGFRcystatin and eGFRcreatinine of >30%, calculated from simultaneously measured serum creatinine and cystatin C levels using the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equations[2,3]. We will define "lower eGFRcystatin than eGFRcreatinine" as CKD-EPI 2012 eGFRcystatin <0.7* CKD-EPI 2021 eGFRcreatinine. In sensitivity analyses, we may look at the difference as continuous or with alternative threshold values.

Outcomes: Incident: 1) all-cause mortality, 2) ESKD; 3) AKI; 4) heart failure; 5) fracture; 6) gout. Incident ESKD is as identified by the US Renal Data System (USRDS) registry[7]. Incident all-cause mortality is as identified by surveillance of the National Death Index[8]. The other outcomes are determined by billing codes from hospitalizations (AKI, heart failure, fracture) or a combination of billing codes and self-report (gout).

Statistical Analysis: We will compare baseline characteristics between those with and without lower eGFRcystatin than eGFRcreatinine (by 30% as defined above) using descriptive statistics, including means, medians, and proportions. For formal testing, we will use a student's t-test or Wilcoxon rank-sum test for continuous variables and chi-squared or Fisher's exact test for categorical variables. We will then model lower eGFRcystatin than eGFRcreatinine (eGFRcystatin<0.7*eGFRcreatinine) as a binary outcome in a logistic regression on multiple covariates. We will trend the difference between eGFRcystatin and eGFRcreatinine for participants from visit 2 through the most recent administrative censoring date. Consistency will be quantified by the odds ratio between consecutive visits. Cross sectional associations will be examined with metabolic abnormalities as the dependent variable. A linear regression model will be constructed to study the independent cross-sectional associations of visits 2-6 continuous outcomes: 1) hemoglobin, 2) phosphate, 3) FGF-23, 4) PTH, and 5) uric acid levels with lower eGFRcystatin than eGFRcreatinine by 30% at that visit. The model will adjust for age, sex, race, eGFRcreatinine and comorbidities. In sensitivity analyses, we will also explore models that do not adjust for eGFRcreatinine. A Cox proportional hazards model will be constructed to study the independent association of a difference between lower eGFRcystatin than eGFRcreatinine by >30% at visit 2 with incidence of subsequent 1) all-cause mortality, 2) ESKD, 3) AKI and 4) heart failure. Secondary analyses will explore 5) fractures and 6) gout. The model will adjust for covariates and demographics +/- eGFRcreatinine as above.

Limitations: One possible limitation of our study is that serum cystatin C levels may have been calibrated slightly differently at different visits.

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/mantrack/maintain/search/dtSearch.html

_____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)?
No other manuscript proposals on differences in eGFRcreatinine and eGFRcystatin to our knowledge.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X___ Yes ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number*_____)
__X B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _CysC data were funded by ancillary studies at visit 4 (PI:Coresh/Astor, 2006.16); visit 3 (PI:Matsushita, 2017.20); visit 2 (PI:Selvin, 2009.16))

*ancillary studies are listed by number https://sites.cscc.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.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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __**X** No.

References

1. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey-Mims MM, Roberts GV, St Peter WL, Warfield C, Powe NR. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. Am J Kidney Dis. 2021 Sep 23:S0272-6386(21)00828-3. doi: 10.1053/j.ajkd.2021.08.003. Epub ahead of print. PMID: 34563581.
2. 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; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012 Jul 5;367(1):20-9. doi: 10.1056/NEJMoa1114248. Erratum in: N Engl J Med. 2012 Aug 16;367(7):681. Erratum in: N Engl J Med. 2012 Nov 22;367(21):2060. PMID: 22762315; PMCID: PMC4398023.
3. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006. Erratum in: Ann Intern Med. 2011 Sep 20;155(6):408. PMID: 19414839; PMCID: PMC2763564.
4. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med. 2006 Jun 8;354(23):2473-83. doi: 10.1056/NEJMra054415. PMID: 16760447.
5. Inker LA, Titan S. Measurement and Estimation of GFR for Use in Clinical Practice: Core Curriculum 2021. Am J Kidney Dis. 2021 Nov;78(5):736-749. doi: 10.1053/j.ajkd.2021.04.016. Epub 2021 Sep 11. PMID: 34518032.
6. Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, Levey AS, Gansevoort RT; CKD Prognosis Consortium. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013 Sep 5;369(10):932-43. doi: 10.1056/NEJMoa1214234. PMID: 24004120; PMCID: PMC3993094.
7. www.usrds.org.
8. Data Access - National Death Index (cdc.gov)