ARIC Manuscript Proposal #4173

PC Reviewed: 12/13/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Risk implications of new estimating equations for GFR with creatinine and/or cystatin C

b. Abbreviated Title (Length 26 characters): Risks using new eGFR equations

2. Writing Group:

Writing group members: Morgan Grams, Josef Coresh, Yingying Sang, Shoshana Ballew, Kunihiro Matsushita, and others for the CKD Prognosis Consortium

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MG___ **[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:

Data analysis will start immediately. A manuscript is expected to be prepared within 6 months.

4. Rationale:

The CKD Prognosis Consortium (CKD-PC) in an international consortium established in 2009 after a controversies conference sponsored by the Kidney Disease: Improving Global Outcomes (KDIGO). Since then CKD-PC has been aiming to conduct sophisticated meta-analyses to inform CKD clinical guidelines and improve CKD clinical practice and research. Indeed, several articles from CKD-PC have been cited in the KDIGO 2012 clinical guidelines for CKD and create a basis for new CKD staging system based on both glomerular filtration rate (GFR) and

albuminuria. CKD-PC will continue to explore clinically important questions surrounding nephrology care.

GFR estimation equations using serum creatinine, e.g., the MDRD Study or the CKD-EPI equations, have been commonly used in clinical practice and epidemiologic studies.[1] Newer estimation equations using cystatin C with and without serum creatinine have been created and evaluated in previous CKD-PC work.[2,3] The CKD Prognosis Consortium provides a great opportunity to evaluate how the new recommended 2021 eGFR equations predict subsequent clinical outcomes of interest. This builds on the foundational work of the CKD-PC developing heat maps as part of the KDIGO 2012 CKD staging and categorization and expanding to new outcomes of interest. **ARIC contributes excellent data on serum creatinine, cystatin C, and risk of subsequent events.**

5. Main Hypothesis/Study Questions:
Estimated eGFR and albuminuria predict subsequent all-cause mortality, cardiovascular mortality (CVM), kidney failure requiring replacement therapy (KFRT), acute kidney injury (AKI), hospitalization, coronary heart disease (CHD), stroke, heart failure (HF), atrial fibrillation, and peripheral artery disease (PAD). Furthermore, the heat map concept of CKD staging with higher risk related to both lower eGFR and higher albuminuria applies to the 2021 CKD-EPI equations and all of these outcomes.

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 population:
All ARIC participants with data of estimated glomerular filtration rate (eGFR) and albuminuria will be included.

Exposures:
- Kidney measures
    - Serum creatinine and cystatin C for use in 2021 CKD-EPI equations (eGFRcr, eGFRcys, eGFRcr-cys).[1,2] We may compare results to older equations but the emphasis is on the utility of the newest, recommended race-free eGFR equations.
    - Albuminuria (urinary albumin-to-creatinine ratio). Albuminuria will be expressed as urinary albumin-to-creatinine ratio (ACR)

Interacting/Confounding Variables:
- Demographics: Age, sex, race
- Medical history/comorbidities: history of cardiovascular disease (myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, stroke, or peripheral artery disease), hypercholesterolemia, hypertension, diabetes mellitus
- Laboratory variables: cholesterol levels (total, HDL, LDL), triglycerides, glucose levels with fasting status, smoking (current, former, never), hemoglobin
- Vital measurements: systolic blood pressure, diastolic blood pressure, anthropometry (BMI [height, weight], waist circumference)

- Interfering medication: antihypertensive medications including ACE inhibitors /ARB, cholesterol-lowering medication (Statins), as well as glucose lowering medication.

Outcome variables:

- All-cause mortality
- Cardiovascular mortality (death from myocardial infarction, heart failure, stroke)
- KFRT (initiation of dialysis, kidney transplantation, death coded due to kidney disease)
- AKI
- Any hospitalization
- CHD
- Stroke
- HF
- Atrial fibrillation
- PAD

Brief analysis plan and methods:

Various cohorts from North America, Europe, Asia, and Australia will be meta-analyzed using a 2-stage approach where each cohort is analyzed and then results are pooled using inverse variance weights (and multi-variate approaches) to create an individual participant level meta-analysis. Participating cohorts are required to send data to the CKD-PC data coordination center, that is, Johns Hopkins University, Baltimore, MD. The data to be sent should not contain identifiers that can identify the individual study participants. We have IRB approval for our analyses.

We will evaluate the associations of eGFR and albuminuria (in continuous and categorical analyses) with the outcomes noted above. Continuous analyses typically use a piece-wise linear spline for eGFR with knots at 60, 90 and 120 ml/min/1.73m^2. Log ACR is modeled linearly. Deviations from model assumptions are tested. Models are constructed based on prior knowledge from the literature (which was used to select the variables listed above) and then tested for adherence to assumptions (e.g. linearity and additivity).

Heat maps will be generated categorically using the KDIGO criteria for eGFR and ACR. We will also compare the goodness of fit of a continuous model with spline (as well as a model with eGFR*ACR interactions) to the categorical model. We will compare the magnitude of the eGFR <60 and ACR coefficients across outcomes to provide a summary of how the strengths of associations varies across outcomes.

Prediction models will be evaluated for discrimination and calibration. Discrimination will be evaluated using the C-statistic as well as the ratio of the predicted risk in the top to bottom decile. Calibration will be tested using the Hosmer-Lemeshow chi-square and the slope of the observed vs. predicted risk in percentile categories (slope of 1.0 indicates perfect calibration). Slopes have the advantage of allowing for meta-analysis and quantifying the calibration.

Models will also consider potential application. In particular, U-shaped relationships which may reflect non-causal associations, outliers and the effect of concurrent medications (e.g. ACEI,

ARB) will be important to scrutinize. Limitations inherent to inferences from observational data including residual confounding, measurement error and selection will be noted.

Summary/conclusion:
By meta-analyzing various cohorts using individual participant level data and the same models; we will be able to rigorously assess the contribution of updated CKD staging (including ACR and 2021 eGFR) to risk. These results will serve as key work for future guidelines and patient care. ARIC would be valuable for appropriate inference in this population.

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 _X___ 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.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)?

The most related manuscript proposals are from the original work MP1123 and 1362, and some with 1754, but these previous proposals did not specifically examine the new eGFR equation.

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 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.

References

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* May 5 2009;150(9):604-612.

2. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* Jul 5 2012;367(1):20-29.

3. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med.* Sep 5 2013;369(10):932-943.