ARIC Manuscript Proposal # 1822

PC Reviewed: 8/9/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Risk implications of various creatinine and cystatin C based glomerular filtration rate estimation equations. Pooled analysis of general population cohorts.

b. Abbreviated Title (Length 26 characters): Various eGFR equations & risk

2. Writing Group:

Writing group members:

Kunihiro Matsushita, Ron Gansevoort, Brad C. Astor, Mark Woodward, Josef Coresh, and others for the CKD prognosis consortium.

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

F**irst author**: **Kunihiro Matsushita, MD, PhD**

Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Welch Center for Prevention, Epidemiology, and Clinical Research
2024 E Monument Street, 2-600
Phone: (410)502-2051 Fax: (410)955-0476
E-mail: kmatsush@jhsph.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, MD, PhD, MHS**

Address: 2024 E. Monument, Suite 2-630
Baltimore, MD 21287
Phone 410-955-0495, Fax 410-955-0476
Email: coresh@jhu.edu

3. Timeline:

Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

In 2002, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) defined and classified chronic kidney disease (CKD).[1] CKD has been defined

as either urinary albumin excretion of ≥30mg/day or a decreased renal function (glomerular filtration rate [GFR] <60 ml/min/1.73 m^2). Approximately 10-16% of the general population is estimated to have CKD.[2] The prevalence of CKD is especially high in the elderly, affecting >40% of people over the age of 70 years.[2]

Since the development of CKD staging system in 2002,[1] there has been increasing recognition of limitations of the definition and classification of CKD, leading to a heated debate and calls for revisions.[3] As a result, Kidney Disease: Improving Global Outcomes (KDIGO) initiated a collaborative meta-analysis and sponsored a controversies conference in October 2009 to examine the relationship of eGFR and albuminuria to mortality and kidney outcomes, which resulted in the CKD prognosis consortium.[3] The CKD Prognosis Consortium published 4 meta-analyses papers based on 45 cohorts that included 1,555,332 participants from general, high-risk, and kidney disease populations.[4-7] These meta-analysis results suggest that the CKD definition should remain the same and the classification of CKD staging should be modified by adding albuminuria stage and subdividing stage 3 CKD (eGFR 30-59 ml/min/1.73m2) into 3a (45-59) and 3b (30-44). These results have been provided to the KDIGO CKD Definition and Classification working group appointed by KDIGO and would be utilized to revise the current CKD definition and staging.[1,3]

The Modification of Diet in Renal Disease (MDRD) Study equation, most commonly used equation in clinical practice and epidemiologic studies for eGFR,[8] was used for the first four meta-analysis papers from CKD Prognosis Consortium. However, recently, several newer estimation equations were developed that are based on serum creatinine, cystatin C or both.[9,10] As compared to the MDRD equation, these new equations seem to perform better in terms of estimating GFR and predicting long-term renal and cardiovascular risk.[11-13] The CKD Prognosis Consortium would provide a great opportunity to evaluate whether these newer GFR equations perform better than the MDRD equation in terms of risk prediction across wide range of populations. The long-term goal of the Consortium includes development of clinically applicable risk-prediction instruments for the onset, progression, and complications of CKD. Current proposal is part of the CKD Prognosis Consortium second phase analyses.

5. Main Hypothesis/Study Questions:

The newly developed creatinine, cystatin C or the combination of creatinine and cystatin C based GFR equations will likely predict long-term cardiovascular disease/mortality and kidney disease progression better than the widely used MDRD Study equation.[8-10] These comparisons will be conducted in the ARIC study which will then be meta-analyzed with other cohorts through the CKD-Prognosis Consortium.

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).

Data:

Exposure Variables from Year 9 (1996-7):

- eGFR (serum creatinine, serum cystatin C). eGFR will be assessed by various estimation equations, that is , creatinine based (MDRD, CKD-EPI), cystatin C based or the combination of creatinine and cystatin based equations.[8-10]

Confounding/Interacting Variables from Year 9 (1996-7) or closest exam:

- Age, sex, race
- Albuminuria (urinary albumin-to-creatinine ratio). Albuminuria will be expressed as urinary albumin-to-creatinine ratio (ACR).
- Other established cardiovascular risk factors: history of cardiovascular disease (myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure or stroke), dummy variable hypercholesterolemia, cholesterol levels (total, HDL, LDL), triglycerides, diabetes mellitus, fasting glucose levels, smoking (current, former, never), BMI (height, weight),hypertension, systolic blood pressure, diastolic blood pressure.
- Interfering medication (blood pressure including ACE inhibitors /ARB, Statins, as well as glucose lowering medication).

Outcome Variables:

- All cause mortality + Follow-up time.
- Cardiovascular mortality (death from myocardial infarction, sudden cardiac death, heart failure, stroke) + Follow-up time
- End-stage renal disease (initiation of dialysis, kidney transplantation, death coded due to kidney disease) + Follow-up time
- Acute kidney injury (Acute initiation of dialysis or ICD-9 code 584) + follow-up time
- Progression of CKD (an average annual decline in eGFR during follow-up of at least 2.5 ml/min/1.73m^2 per year and a last eGFR value being less than 45 ml/min/1.73m^2)

Analysis plan and methods:

Various cohorts from North America, Europe, Asia, and Australia will be analyzed using individual participant level data. Results will then be compared using Forest Plots and meta-analyzed. ARIC will provide useful information on a general population based sample of adults studied rigorously.

GFR will be estimated by MDRD, CKD-EPI, Cystatin C and combination of Cystatin C and creatinine based equations.[8-10] The primary analysis will use Cox proportional hazards models. Both continuous and categorical representations of eGFR and albuminuria will be explored. Moreover, net reclassification of each CKD-Epi, Cystatin C and the combination of Cystatin C and creatinine based equations will be compared to MDRD equation.[14]

A. First, we will use categorical analysis, with CKD being defined according to the clinically relevant categories that were evaluated in the phase 1 meta-analysis of the CKD-PC collaboration:

- eGFR > 105

- eGFR 90–105 (reference category)
- eGFR 75–90
- eGFR 60–75
- eGFR 45–60
- eGFR 30–45
- eGFR 15–30
- eGFR <15, because the expected number of subjects in this category will probably very low, these individuals might be excluded from the analysis.

B. We will evaluate the continuous association of eGFR, using various equations, with incidence rates of clinical outcomes using Cox proportional hazard models incorporating spline terms for eGFR with knots at 45, 60, 75, 90 and 105 mL/min/1.73 m^2 with and without adjustment for age, sex, race and classical atherosclerosis risk factors. Any potential interaction of eGFR with albuminuria and other cardiovascular risk factors will be considered in the analyses.

C. Reclassification will be assessed for each of the above mentioned categories of eGFR, comparing CKD-Epi, cystatin C and combined cystatin C and creatinine based equations to the MDRD equation. We will assess whether risk of clinical outcomes differ between participants reclassified versus those not reclassified. To further evaluate overall improvement in reclassification, we will calculate net reclassification improvement,[14] calculated as the sum of the proportion of participants reclassified downward to a lower eGFR category in individuals with an outcome and the proportion of participants reclassified upward to a higher eGFR category in individuals without an outcome, less the sum of the proportion of participants reclassified upward in individuals with an outcome and the proportion of participants reclassified downward in individuals without an outcome. This calculation represents the sum of the 2 terms corresponding to "clinically correct" reclassification minus the 2 terms reflecting "clinically incorrect" reclassification.

Summary/conclusion:

By pooling data from more than 1.5 million, from all over the world, on individual participant level; we will be able to identify the eGFR equation that the best reflects cardiovascular and renal prognosis. The results of this analysis will presumably lead to substitution of the MDRD equation by a better eGFR equation in all settings, including the daily patient care. Given that more than 200 million estimated GFR results are reported each year in the US, our analysis would be clinical relevant and may result in better patient care and resource allocation.

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 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 __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)?

MP1423: Cystatin C-based estimated GFR and albuminuria as predictors of coronary heart disease (CHD) events and mortality; Astor, B.

MP1449: Comparison of a novel equation for estimated glomerular filtration rate with a conventional one regarding the association with coronary heart disease, stroke, and all-cause mortality: The Atherosclerosis Risk in Communities (ARIC) Study; Matsushita, K.

These are the most relevant proposals and the key authors of each proposal are included in this proposal.

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/

12. 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.

References:

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39: S1–266.

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5. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011; (in press)

6. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int. 2011; (in press)

7. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int. 2011; (in press)

8. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145: 247–54.

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10. Stevens LA, Coresh J, Schmid CH et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis. 2008;51:395-406.

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12. Matsushita K, Selvin E, Bash LD, et al. Risk Implications of the New CKD Epidemiology Collaboration (CKD-EPI) Equation Compared With the MDRD Study Equation for Estimated GFR: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis.2010;55:648-659.

13. Peralta CA, Katz R, Sarnak MJ, et al. Cystatin C identifies chronic kidney disease patients at higher risk for complications. J Am Soc Nephrol. 2011;22:47-55.

14. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008;27:157-172; discussion 207-112.