1.a. Full Title: 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

b. Abbreviated Title (Length 26 characters): CKD-EPI vs. MDRD formula & CVD

2. Writing Group:

Writing group members:
Kunihiro Matsushita, MD, PhD; Elizabeth Selvin, PhD, MPH; Lori D. Bash, MPH; Brad Astor, PhD, MPH; Josef Coresh, MD, PhD; others welcome.

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]

First 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: Elizabeth Selvin PhD, MPH
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) 614-3752  Fax: (410)955-0476
E-mail: lselvin@jhsph.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:**

Numerous articles have reported that reduced glomerular filtration rate (GFR) is a predictor of incident cardiovascular disease (CVD) [1-14]. Consequently, individuals with impaired GFR, even at moderate levels, are placed in the highest risk group for CVD in clinical guidelines [15,16].

Currently, the Modification of Diet in Renal Disease (MDRD) equation is the conventional formula used in clinical practice to estimate GFR. However, the MDRD formula has been shown to be relatively imprecise in individuals with GFR higher than 60 ml/min/1.73m² [5], potentially resulting in misclassification of risk for future cardiovascular events.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) group soon will publish a novel equation designed to improve the estimation of GFR, particularly among individuals with normal or mildly impaired kidney function. However, it is unknown whether a classification based on this novel CKD-EPI equation is more strongly associated with future CVD events than the MDRD equation.

Therefore, the objective of this study is to compare the CKD-EPI and the MDRD equation regarding their associations with CVD and all-cause mortality in the ARIC Study.

5. **Main Hypothesis/Study Questions:**

**Hypothesis:** The classification of kidney function according to the CKD-EPI equation will be more strongly associated with incident CVD and all-cause mortality than the same categorization scheme using the MDRD equation.

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).**

**Inclusions:**
All black and white ARIC subjects with measured serum creatinine, and other variables (age, sex) required for the estimation of GFR.

**Exclusions:**
Ethnicity other than black or white
Individuals missing data required to estimate GFR

**Exposure:** GFR estimated by the CKD-EPI and the MDRD equations

Kidney function will be estimated using both the CKD-EPI and the simplified version of MDRD equation incorporating data of serum creatinine concentration, age, gender, and race from visit 1 and measured in ml/min/1.73m².

**Outcome:**
Incident coronary heart disease (CHD) including a hospitalized myocardial infarction, fatal CHD, or cardiac procedures, stroke, and all-cause death through 2004

**Covariates:**
Sociodemographics: age, race, gender, education
Physical information: blood pressure, body mass index
Lifestyle: smoking status and alcohol habit
Comorbidities: hypertension, diabetes, dyslipidemia, history of CVD
Statistical Analysis Plan:
First, we will compute incidence rates for CVD and all-cause mortality among clinical categories of GFR 1) <30, 2) 30 to 59, 3) 60 to 89, 4) \( \geq 90 \) ml/min/1.73m\(^2\) calculated based on both equations and compare their trends.

Then, we will compare the equations across above clinical categories of GFR, classifying participants using a 4*4 table according to these categories. We will compare incidence rates of CVD and all-cause death in the different CKD-EPI GFR groups among a given MDRD GFR stratum and vice versa. Through this analysis, we will be able to identify the proportion of individuals reclassified by the CKD-EPI equation compared to the MDRD equation. Moreover, we will calculate the net reclassification index (NRI) proposed by Penicina MJ, et al. [17] as a measure of relevant change in these clinical categories [18]. The NRI is the difference in proportions moving up and down among individuals with and without outcomes and allows us to estimate the statistical significance about clinical relevance of observed reclassification [18].

We will conduct subgroup analyses stratifying subjects according to race and gender, since dissimilar indices used for race and gender in the equations may affect the results.

Limitations:
Of the ARIC participants, only 3% had GFR less than 60 ml/min/1.73m\(^2\) at visit 1. So, statistical power to detect any difference between the two equations in this group with low kidney function will be limited. However, since CKD-EPI equation was initiated aiming at better estimation of GFR above 60, results obtained by this cohort are particularly important.

Also, the CKD-EPI equation was compared to the MDRD equation but not a “gold standard” measurement of GFR. However, measurement of GFR is considered cumbersome and expensive and is not usually performed in routine clinical practice or population-based research, and, thus, the MDRD equation conventionally has been used to estimate GFR in those circumstances [19]. Therefore, these data reflect a realistic clinical scenario.

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
8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?

____ 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)?

#172: Levels of Albumin, Creatinine, and Incident Coronary Heart Disease; Heiss, G
#758: Serum creatinine and risk of CVD: Atherosclerosis Risk in Communities (ARIC) Study; Ibrahim H
#952: Kidney function and anemia as risk factors for coronary heart disease and mortality: The ARIC Study; Astor, BC
#1028: Cardiovascular risk among adults with chronic kidney disease, with or without prior myocardial infarction; Wattanakit, K
#1058: Kidney Function and Risk of Peripheral Arterial Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study; Wattanakit, K
#1118: Reduced Kidney Function as a risk factor for incident heart failure: The ARIC Study; Kottgen, A
#1244: Kidney Dysfunction and Sudden Cardiac Death among Participants in the ARIC Study; Deo, R
#1348: Chronic kidney disease and risk of hospitalization: The Atherosclerosis Risk in Communities Study; Bash, LD

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


