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

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Background: The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recently published an equation for estimated glomerular filtration rate (eGFR) using the same variables (serum creatinine level, age, sex, and race) as the Modification of Diet in Renal Disease (MDRD) Study equation. Although the CKD-EPI equation estimates GFR more precisely compared with the MDRD Study equation, whether this equation improves risk prediction is unknown.

Study Design: Prospective cohort study, the Atherosclerosis Risk in Communities (ARIC) Study.

Setting & Participants: 13,905 middle-aged participants without a history of cardiovascular disease with median follow-up of 16.9 years.

Predictor: eGFR.

Outcomes & Measurements: We compared the association of eGFR in categories (≥120, 90-119, 60-89, 30-59, and <30 mL/min/1.73 m^2) using the CKD-EPI and MDRD Study equations with risk of incident end-stage renal disease, all-cause mortality, coronary heart disease, and stroke.

Results: The median value for $eGFR_{CKD-EPI}$ was higher than that for $eGFR_{MDRD}$ (97.6 vs 88.8 mL/min/1.73 m^2; $P < 0.001$). The CKD-EPI equation reclassified 44.9% (n = 3,079) and 43.5% (n = 151) of participants with $eGFR_{MDRD}$ of 60-89 and 30-59 mL/min/1.73 m^2, respectively, upward to a higher eGFR category, but reclassified no one with $eGFR_{MDRD}$ of 90-119 or <30 mL/min/1.73 m^2, decreasing the prevalence of CKD stages 3-5 from 2.7% to 1.6%. Participants with $eGFR_{MDRD}$ of 30-59 mL/min/1.73 m^2 who were reclassified upward had lower risk compared with those who were not reclassified (end-stage renal disease incidence rate ratio, 0.10 [95% CI, 0.03-0.33]; all-cause mortality, 0.30 [95% CI, 0.19-0.48]; coronary heart disease, 0.36 [95% CI, 0.21-0.61]; and stroke, 0.50 [95% CI, 0.24-1.02]). Similar results were observed for participants with $eGFR_{MDRD}$ of 60-89 mL/min/1.73 m^2. More frequent reclassification of younger, female, and white participants explained some of these trends. Net reclassification improvement in participants with eGFR < 120 mL/min/1.73 m^2 was positive for all outcomes ($P < 0.001$).

Limitations: Limited number of cases with eGFR < 60 mL/min/1.73 m^2 and no measurement of albuminuria.

Conclusions: The CKD-EPI equation more appropriately categorized individuals with respect to long-term clinical risk compared with the MDRD Study equation, suggesting improved clinical usefulness in this middle-aged population.

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INDEX WORDS: Estimated glomerular filtration rate; cardiovascular disease; end-stage renal disease; epidemiology.

Editorial, p. 622

Glomerular filtration rate (GFR) is the best overall measure of kidney function.[1] However, direct measurement of GFR using radioactive agents is burdensome and expensive.[1] Thus, equations for estimated GFR (eGFR) using endogenous filtration markers such as serum creatinine have been developed and used for chronic kidney disease (CKD) diagnosis and staging.[2] The Modification of Diet in Renal Disease (MDRD) Study equation, which incorporates information about age, sex, race, and serum creati-

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nine concentration, is most commonly used in clinical practice and epidemiologic studies to estimate kidney function.[3-6]

Despite its widespread use, eGFR using the MDRD Study equation ($eGFR_{MDRD}$) has several limitations. The MDRD Study equation was developed in a population of individuals with CKD and decreased GFR[7,8] and systematically underestimates GFR in individuals with measured GFR $\geq$ 60 mL/min/1.73 m^2.[8-10] Previous studies have suggested that use of the MDRD Study equation may result in "overdiagnosis" of CKD.[8,9,11]

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recently published a new equation to improve the estimation of GFR, particularly in individuals with GFR $\geq$ 60 mL/min/1.73 m^2.[12] The CKD-EPI equation was developed using data from 8,254 individuals from 10 studies, including the MDRD Study, and validated in an additional 16 studies containing 3,896 individuals.[12] eGFR using the CKD-EPI equation ($eGFR_{CKD\text{-}EPI}$) was more accurate at estimating measured GFR overall and in individuals with normal or mildly decreased kidney function compared with $eGFR_{MDRD}$. Importantly, CKD prevalence was decreased from 13.1% based on the MDRD Study equation to 11.5% using the CKD-EPI equation in the adult US population represented by the National Health and Nutrition Examination Survey 1999-2006.[12]

However, performance of the CKD-EPI equation for classification of long-term clinical risk has not been evaluated. The objective of this study is to evaluate the implications of eGFR categories based on the CKD-EPI equation compared with those based on the conventional MDRD Study equation for classifying individuals at risk of end-stage renal disease (ESRD), all-cause mortality, coronary heart disease (CHD), and stroke.

METHODS

Study Population

We analyzed data from participants in the Atherosclerosis Risk in Communities (ARIC) Study, a population-based cohort study of middle-aged individuals from 4 US communities: Forsyth County, NC; suburban Minneapolis, MN; Washington County, MD; and Jackson, MS. Details of the ARIC Study are described elsewhere.[13] In brief, 15,792 men and women aged 45-64 years were enrolled from 1987 through 1989. In the present study, we excluded participants self-reporting race other than white or black (n = 48) or missing serum creatinine values at baseline (n = 150). We also excluded participants with a history of cardiovascular disease at baseline based on self-report or clinical examination or missing data for cardiovascular history (n = 1,726), for a final study population of 13,905 participants. As might be expected, participants who were excluded because of a history of cardiovascular disease (n = 1,038) had a poorer risk-factor profile compared with the final study population (mean age, 57.0 vs 54.0 years; systolic blood pressure, 124.1 vs 121.1 mm Hg; and low-density lipoprotein cholesterol level, 147.4 vs 136.7 mg/dL). Participants excluded because of missing information (n = 801) were similar to the final study population (mean age, 54.2 years; systolic blood pressure, 122.6 mm Hg; and low-density lipoprotein cholesterol level, 142.8 mg/dL).

Data Collection

ARIC Study participants provided information for baseline demographic and behavioral variables and medical history to a trained interviewer. Completed years of education and smoking status (current or former/never) were determined by self-report. Blood samples were collected according to standardized procedures.[14] Certified technicians measured systolic and diastolic blood pressures with participants in the sitting position after 5 minutes of rest using a random-zero sphygmomanometer. The average of the second and third readings was recorded. We defined diabetes mellitus as a fasting glucose level $\geq$ 126 mg/dL, nonfasting glucose level $\geq$ 200 mg/dL, self-reported physician diagnosis of diabetes, or use of oral hypoglycemic medication or insulin. Plasma cholesterol, triglyceride, and high-density lipoprotein cholesterol levels were determined using enzymatic methods, and low-density lipoprotein cholesterol level was calculated using the Friedewald equation.[14] Left ventricular hypertrophy by electrocardiogram was defined using the Cornell voltage.[15] Evidence of atherosclerosis of the common carotid arteries (shadowing/plaque on either side) was determined using ultrasound examination.[13,16]

Estimation of GFR

Serum creatinine was measured using a modified kinetic Jaffé method[14,17] and corrected for interlaboratory differences, calibrated to the Cleveland Clinic by subtraction of 0.24 mg/dL[16,18] and standardized to the Roche enzymatic method (Roche-Hitachi PModule instrument with Roche Creatininase Plus assay, Hoffman-La Roche Ltd, www.roche.com) by multiplication of 0.95.[19] We calculated eGFR using the isotope dilution mass spectrometry (IDMS)-traceable 4-variable MDRD Study equation: $eGFR_{MDRD} = 175 \times (\text{standardized serum creatinine [mg/dL]})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$[7,20] and also using the CKD-EPI equation: $eGFR_{CKD\text{-}EPI} = 141 \times (\text{minimum of standardized serum creatinine [mg/dL]}/\kappa \text{ or } 1)^{\alpha} \times (\text{maximum of standardized serum creatinine [mg/dL]}/\kappa \text{ or } 1)^{-1.209} \times 0.993^{\text{age}} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$, where κ is 0.7 if female and 0.9 if male and α is -0.329 if female and -0.411 if male.[12] The unique properties of the CKD-EPI equation compared with the MDRD Study equation include a steeper gradient for age, a less steep slope for

serum creatinine level < 0.7 mg/dL in females and 0.9 mg/dL in males and a similarly steep slope at a range higher than these levels, a smaller black-white ratio, and a slightly higher female-male ratio, particularly when creatinine concentration is < 0.9 mg/dL.[12] These properties resulted in higher $eGFR_{CKD\text{-}EPI}$ compared with $eGFR_{MDRD}$, particularly in a younger population, females, and whites.[12]

Outcome Assessment

ARIC investigators conduct continuous comprehensive surveillance for all cardiovascular disease–related hospitalizations and deaths in the 4 communities. All potential cardiovascular events are adjudicated using published criteria.[21-23] We defined incident CHD as definite or probable myocardial infarction, definite coronary death, or coronary revascularization procedure. Stroke included definite or probable cases defined as sudden or rapid onset of neurologic symptoms that lasted for 24 hours or led to death in the absence of another cause.[22,23]

ESRD cases included all participants with a history of hospitalization with an *International Classification of Diseases* Ninth or Tenth Revisions code specified for kidney transplant, dialysis, or a procedure indicating dialysis and for individuals with an earlier diagnosis of CKD and underlying cause of death of acute renal failure. Individuals with a code of traumatic anuria or those with a transplant or dialysis code on the same date as another code for acute renal failure (*International Classification of Diseases, Ninth Revision* codes 586, 584, and 788.9) but without previous CKD were not included.

Statistical Analyses

We categorized eGFR using the following clinically relevant cutoff values established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI): ≥120, 90-119, 60-89, 30-59, and <30 mL/min/1.73 m^2.[3] Participants with eGFR < 15 mL/min/1.73 m^2 (CKD stage 5) were not considered separately in the present study because there were few participants in this category (n = 16 for $eGFR_{CKD\text{-}EPI}$ and n = 15 for $eGFR_{MDRD}$). Individuals with eGFR ≥ 120 mL/min/1.73 m^2 were considered separately from those with eGFR of 90-119 mL/min/1.73 m^2 under the assumption that high eGFR may result from very low creatinine levels because of muscle loss related to ill health and may not necessarily be associated with better long-term outcomes.[16,24] We compared baseline characteristics of the population across these eGFR categories.

We evaluated the continuous association between eGFR using both equations and incidence rates of clinical outcomes using a Poisson regression model incorporating linear spline terms for eGFR (knots at 45, 60, 75, 90, and 105 mL/min/1.73 m^2) with and without adjustment for age, sex, and race. We also evaluated the risk of clinical outcomes according to categories of eGFR using eGFR of 90-119 mL/min/1.73 m^2 as the reference group and after adjusting for multiple covariates. Model discrimination was assessed using Harrell's C statistic.[25] We defined follow-up time as the period to the first outcome or loss to follow-up. Individuals who were free of these outcomes by January 1, 2006 (January 1, 2005, for ESRD), were subject to administrative censoring.

To assess reclassification, we created a 5×5 cross-tabulation of the $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI}$ categories, calculated the proportion of participants reclassified using $eGFR_{CKD\text{-}EPI}$ in each category of $eGFR_{MDRD}$, and assessed whether risk of clinical outcomes differed between participants reclassified and those not reclassified. To further evaluate overall improvement in reclassification, we calculated net reclassification improvement,[26] 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. In sensitivity analyses, we also assessed net reclassification improvement using 10-year risk categories (<5%, 5% to <10%, 10% to <20%, and ≥20%) of each outcome predicted from Cox proportional hazards models.[27] All analyses were conducted using Stata 10.1 software (Stata Corp, www.stata.com), and $P < 0.05$ is considered statistically significant.

RESULTS

Characteristics of Study Participants

Participants with CKD stage 3 ($eGFR_{CKD\text{-}EPI}$ of 30-59 mL/min/1.73 m^2) or stage 4/5 ($eGFR_{CKD\text{-}EPI}$ < 30 mL/min/1.73 m^2) were more likely to be older, women, and black and have more comorbid conditions, including diabetes, compared with individuals with $eGFR_{CKD\text{-}EPI}$ of 90-119 mL/min/1.73 m^2 (Table 1). The category of $eGFR_{CKD\text{-}EPI}$ ≥ 120 mL/min/1.73 m^2 mainly consisted of black women who also tended to have a higher prevalence of diabetes and left ventricular hypertrophy, more often reported using antihypertensive medications, and had a higher body mass index compared with those with $eGFR_{CKD\text{-}EPI}$ of 90-119 mL/min/1.73 m^2. However, mean age in this group was younger compared with the other categories. Similar results were observed across categories of $eGFR_{MDRD}$ (Table S1; available as online supplementary material associated with this article at www.ajkd.org).

Mean $eGFR_{CKD\text{-}EPI}$ was higher in persons with eGFR of 30-89 mL/min/1.73 m^2, but lower than $eGFR_{MDRD}$ in individuals with eGFR ≥ 120 mL/min/1.73 m^2 (Table 1; Fig 1). Mean $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ were similar for categories of eGFR of 90-119 and < 30 mL/min/1.73 m^2.

Table 1. Characteristics of Participants According to Clinical Categories of $eGFR_{CKD\text{-}EPI}$

Characteristic	Categories of $eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m^2)				
	≥120 (n = 716)	90-119 (n = 9,035)	60-89 (n = 3,931)	30-59 (n = 196)	<30 (n = 27)
Age (y)	49.4 ± 3.9	53.5 ± 5.5	55.5 ± 6.0	58.7 ± 5.3	56.4 ± 6.7
Men	188 (26)	3,791 (42)	1,956 (50)	79 (40)	7 (26)
Black race	679 (95)	2,267 (25)	733 (19)	63 (32)	25 (93)
Educational level completed (y) (n = 13,883)					
<12	253 (35)	2,003 (22)	798 (20)	68 (35)	16 (59)
12-16	224 (31)	3,771 (42)	1,620 (41)	69 (35)	9 (33)
>16	238 (33)	3,246 (36)	1,507 (38)	59 (30)	2 (7)
Current smokers (n = 13,893)	233 (33)	2,545 (28)	761 (19)	45 (23)	5 (19)
Body mass index (kg/m^2) (n = 13,895)	29.9 ± 6.9	27.4 ± 5.4	27.7 ± 4.8	28.5 ± 5.2	29.3 ± 5.5
Diabetes mellitus (n = 13,882)	145 (20)	911 (10)	383 (10)	50 (26)	15 (56)
Antihypertensive medication (n = 13,897)	257 (36)	2,220 (25)	1,230 (31)	124 (63)	18 (67)
Systolic blood pressure (mm Hg) (n = 13,900)	126.6 ± 20.1	120.3 ± 18.4	121.3 ± 18.4	127.6 ± 22.3	153.5 ± 34.0
Diastolic blood pressure (mm Hg) (n = 13,900)	79.2 ± 12.4	73.2 ± 11.1	73.9 ± 10.9	74.9 ± 12.2	80.2 ± 13.3
Low-density lipoprotein cholesterol (mg/dL) (n = 13,625)	127.4 ± 40.7	135.6 ± 38.5	140.4 ± 39.4	147.0 ± 45.4	153.3 ± 67.1
High-density lipoprotein cholesterol (mg/dL) (n = 13,814)	57.2 ± 19.1	52.8 ± 17.1	50.3 ± 16.6	48.1 ± 16.6	48.4 ± 19.5
Triglycerides (mg/dL) (n = 13,815)	111.1 ± 81.8	127.1 ± 87.1	135.2 ± 91.6	165.1 ± 110.1	174.9 ± 145.1
Left ventricular hypertrophy (n = 13,587)	25 (4)	157 (2)	80 (2)	9 (5)	6 (22)
Carotid atherosclerosis (n = 13,473)	46 (7)	603 (7)	338 (9)	26 (14)	7 (30)
Serum creatinine (mg/dL)	0.61 ± 0.10	0.75 ± 0.13	0.96 ± 0.14	1.33 ± 0.24	7.00 ± 5.02
$eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m^2)	125.5 ± 5.3	102.1 ± 7.3	79.8 ± 7.4	53.0 ± 6.3	13.9 ± 10.1
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	139.0 ± 19.4	99.2 ± 13.4	73.5 ± 6.8	50.5 ± 5.8	14.2 ± 9.9

Note: Values expressed as mean ± standard deviation or number (percentage). Conversion factors for units: low- and high-density lipoprotein cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129; creatinine in mg/dL to μmol/L, ×88.4; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations and definitions: $eGFR_{CKD\text{-}EPI}$, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; $eGFR_{MDRD}$, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease (MDRD) Study equation.

Overall, the median value for $eGFR_{CKD\text{-}EPI}$ was higher than that for $eGFR_{MDRD}$ (97.6 [interquartile range, 87.3-105.6] and 88.8 mL/min/1.73 m^2 [interquartile range, 79.8-102.1], respectively; $P < 0.001$). In particular, median $eGFR_{CKD\text{-}EPI}$ was higher than $eGFR_{MDRD}$ in women, whites, and younger individuals (+8.8 mL/min/1.73 m^2 in women vs +6.9 mL/min/1.73 m^2 in men, +10.0 mL/min/1.73 m^2 in whites vs +5.8 mL/min/1.73 m^2 in blacks, and +9.5 mL/min/1.73 m^2 in younger [45-54 y] vs +7.3 mL/min/1.73 m^2 in older persons [55-64 years]), as expected. The distribution of $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ values is shown in Fig 2A.

Incidence Rates According to eGFR Using Each Equation

During a median follow-up of 16.9 years, there were 192 cases of ESRD, 2,478 deaths, 1,863 cases of CHD, and 700 cases of stroke. The continuous relationships between eGFR using both equations and incidence rates of the

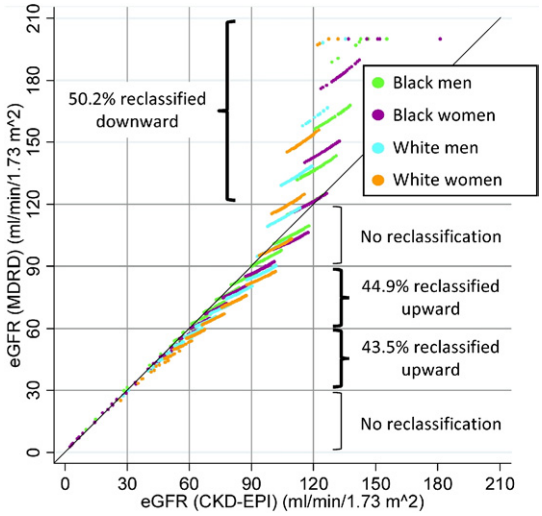

Figure 1. Scatter plot of estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD-EPI}$) and Modification of Diet in Renal Disease Study ($eGFR_{MDRD}$) equations according to the combination of sex and race. Points in off-diagonal boxes indicate individuals who are reclassified into a higher (below the diagonal) or lower (above the diagonal) eGFR category using the $eGFR_{CKD-EPI}$ compared to the $eGFR_{MDRD}$ equation. The graph includes 13,905 individuals but points with the same eGFR plot on top of each other. Individuals with $eGFR_{MDRD} > 200$ mL/min/1.73 m^2 are plotted at 200.

clinical outcomes with and without adjusting for age, sex, and race are shown in Fig 2. Although trends for both equations were similar, incidence rates of the 4 outcomes were higher throughout the range of moderately decreased $GFR_{CKD-EPI}$ compared with the same levels for $eGFR_{MDRD}$. The positive slopes of eGFR with ESRD, all-cause mortality, and stroke at a range of eGFR $>$ 105 mL/min/1.73 m^2 were steeper for $GFR_{CKD-EPI}$ than $eGFR_{MDRD}$. In contrast, CHD risk was lower even at eGFRs $>$ 120 mL/min/1.73 m^2 for $eGFR_{CKD-EPI}$, but not for $eGFR_{MDRD}$.

Adjusted incidence rate ratios for each outcome comparing eGFR categories of the CKD-EPI and MDRD Study equations are listed in Table 2. For both equations, categories of eGFR $<$ 60 mL/min/1.73 m^2 were consistently associated with similarly greater risks of each outcome. Individuals with eGFR of 60-89 mL/min/1.73 m^2 using either equation had higher risks of incident ESRD and stroke compared with the reference groups. Incidence rates of ESRD and all-cause mortality in participants with eGFR $\geq$ 120 mL/min/1.73 m^2 using both equations were significantly higher compared with the reference groups for both equations. Harrell's C statistics were obtained after Cox proportional hazards models with the covariates listed in Table 2 and were nearly identical for $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$ (ESRD, 0.912 vs 0.908; all-cause mortality, 0.746 vs 0.747; CHD, 0.751 vs 0.750; and stroke, 0.760 vs 0.761, respectively).

Although adjusted relative risks are very similar, there was substantial reclassification of individual participants to different eGFR groups. Specifically, the size of the reference group with eGFR of 90-119 mL/min/1.73 m^2 changed dramatically from 4,830 using the MDRD Study equation to 8,357 using the CKD-EPI equation. However, the risk of these groups is similar because the absolute risk of individuals with $eGFR_{CKD-EPI}$ of 90-119 mL/min/1.73 m^2, but $eGFR_{MDRD}$ of 60-89 or $\geq$ 120 mL/min/1.73 m^2, is very similar to individuals with eGFR of 90-119 mL/min/1.73 m^2 using both equations (Table 3).

Cross-Tabulated Incidence Rates According to eGFR Using Both Equations

To directly compare both equations, we computed crude incidence rates of each outcome for cross-categories of $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$ (Table 3). Of 1,439 participants with $eGFR_{MDRD} \geq$ 120 mL/min/1.73 m^2, 50.2% (n = 723) were reclassified downward to the category of eGFR of 90-119 mL/min/1.73 m^2 using the CKD-EPI equation. No one was reclassified using the CKD-EPI equation in participants with $eGFR_{MDRD}$ of 90-119 or $<$ 30 mL/min/1.73 m^2. In contrast, 44.9% (n = 3,079) and 43.5% (n = 151) of participants with $eGFR_{MDRD}$ of 60-89 and 30-59 mL/min/1.73 m^2 were reclassified upward to a higher eGFR category, decreasing the CKD prevalence based on eGFR in our population from 2.7% to 1.6%, respectively.

Importantly, participants who were reclassified upward to a higher eGFR category consistently had a lower risk of all outcomes than those who were unchanged in the same eGFR category. For participants with $eGFR_{MDRD}$ of 30-59 mL/min/1.73 m^2 who were reclassified to $eGFR_{CKD-EPI}$ of 60-89 mL/min/1.73 m^2, the incidence rate ratios compared with those who stayed in the lower category were 0.10 (95% confidence interval [CI], 0.03-0.33) for ESRD (1.3 vs 13.1/

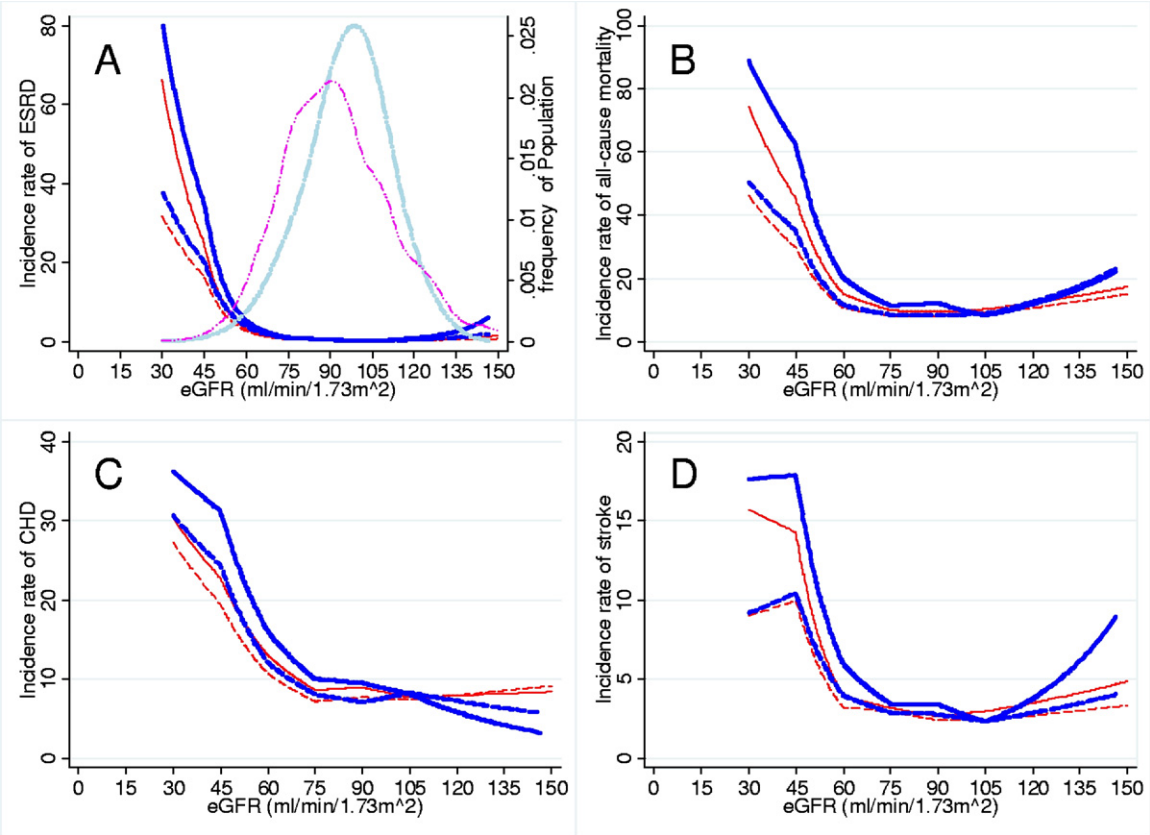

Figure 2. Incidence rates (per 1,000 person-years) of (A) end-stage renal disease (ESRD), (B) all-cause mortality, (C) coronary heart disease, and (D) stroke according to estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD\text{-}EPI}$; blue and thick) and Modification of Diet in Renal Disease Study ($eGFR_{MDRD}$; red) equations without (solid lines) and with (dashed lines) adjustment for mean values of age, sex, and race. (A) The long-dash 2-dot lines show kernel density plots of distributions of $eGFR_{CKD\text{-}EPI}$ (light blue and thick) and $eGFR_{MDRD}$ (magenta).

1,000 person years in Table 3), 0.30 (95% CI, 0.19-0.48) for all-cause mortality, 0.36 (95% CI, 0.21-0.61) for CHD, and 0.50 (95% CI, 0.24-1.02) for stroke. Similar results were observed for participants with $eGFR_{MDRD}$ of 60-89 mL/min/1.73 m^2 (ESRD incidence rate ratio, 0.35 [95% CI, 0.20-0.58]; all-cause mortality, 0.61 [95% CI, 0.54-0.69]; CHD, 0.72 [95% CI, 0.63-0.82]; and stroke, 0.62 [95% CI, 0.49-0.78]). The pattern was less consistent for participants with $eGFR_{MDRD} \geq 120$ mL/min/1.73 m^2 who were reclassified downward to $eGFR_{CKD\text{-}EPI}$ of 90-119 mL/min/1.73 m^2.

Subsequently, we compared age-, sex-, and race-adjusted incidence rates and found that participants reclassified upward using the CKD-EPI equation still tended to have lower risk compared with those who were not reclassified, although this comparison was statistically significant for only ESRD (ESRD incidence rate ratio, 0.55 [95% CI, 0.31-0.95] for $eGFR_{MDRD}$ of 60-89 mL/min/1.73 m^2 and 0.13 [95% CI, 0.04-0.47] for $eGFR_{MDRD}$ of 30-59 mL/min/1.73 m^2; all-cause mortality, 0.94 [95% CI, 0.82-1.08] and 0.72 [95% CI, 0.42-1.23]; CHD, 0.94 [95% CI, 0.82-1.08] and 0.78 [95% CI, 0.41-1.47]; and stroke, 0.95 [95% CI, 0.74-1.22] and 0.95 [95% CI, 0.40-2.28], respectively).

Net Reclassification Improvement

The analysis of net reclassification improvement based on eGFR categories was conducted after excluding participants with either $eGFR_{CKD\text{-}EPI}$ or $eGFR_{MDRD} \geq 120$ mL/min/1.73 m^2 because reclassification to lower values from this group has a different meaning because of the J-shaped

Table 2. Adjusted Incidence Rate Ratio for Outcomes According to eGFR Categories Determined Using Either the CKD-EPI or MDRD Study Equation

	Categories of eGFR (mL/min/1.73 m^2)				
	≥120	90-119	60-89	30-59	<30
No. of participants					
CKD-EPI[a]	641	8,357	3,645	171	21
MDRD[a]	1,297	4,830	6,380	307	21
Outcomes					
ESRD					
CKD-EPI	2.07 (1.13-3.79)	(reference)	2.89 (1.94-4.30)	16.70 (10.13-27.53)	54.43 (26.69-111.00)
MDRD	2.04 (1.13-3.67)	(reference)	2.85 (1.80-4.50)	16.09 (9.33-27.75)	59.06 (28.17-123.81)
All-cause mortality					
CKD-EPI	1.34 (1.10-1.64)	(reference)	1.01 (0.91-1.11)	1.69 (1.33-2.15)	5.53 (3.48-8.80)
MDRD	1.27 (1.10-1.47)	(reference)	0.99 (0.90-1.09)	1.56 (1.25-1.93)	5.54 (3.48-8.81)
CHD					
CKD-EPI	0.83 (0.61-1.12)	(reference)	1.01 (0.91-1.12)	1.46 (1.08-1.97)	2.20 (0.90-5.34)
MDRD	1.06 (0.88-1.29)	(reference)	1.00 (0.90-1.11)	1.29 (0.99-1.68)	2.25 (0.92-5.46)
Stroke					
CKD-EPI	1.12 (0.80-1.58)	(reference)	1.17 (0.98-1.40)	1.71 (1.09-2.67)	1.77 (0.56-5.61)
MDRD	1.14 (0.87-1.49)	(reference)	1.16 (0.97-1.38)	1.88 (1.29-2.75)	1.81 (0.57-5.76)

Note: Values in parentheses are 95% confidence intervals. Adjusted for following covariates: age, race, sex, level of education, systolic blood pressure, antihypertensive medication, diabetes, smoking, body mass index, low- and high-density lipoprotein cholesterol levels, left ventricular hypertrophy, and carotid atherosclerosis.

Abbreviations: CHD, coronary heart disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; ESRD, end-stage renal disease; MDRD, Modification of Diet in Renal Disease.

[a]Participants included in the fully adjusted analysis.

associations of eGFR with risk. The detailed table for calculating net reclassification improvement for incident ESRD is listed in Table 4 (Tables S2-S4 for the other outcomes). Of 170 participants who had incident ESRD during follow-up, 12.4% (n = 21) were reclassified incorrectly to a lower risk (higher eGFR) category using the CKD-EPI equation. However, in 12,230 participants who were free of ESRD during follow-up, 26.1% (n = 3,193 participants) were reclassified correctly to a lower risk (higher eGFR) group. In sum, net reclassification improvement for ESRD using the CKD-EPI equation was 0.138 ($P < 0.001$). Overall, the CKD-EPI equation was associated with a significantly positive net reclassification improvement for all outcomes (Table S5). Similar results were obtained in subgroups by race, sex, and age (45-54 or 55-64 years), although blacks tended to have lower net reclassification improvements for all outcomes than whites. Net reclassification improvements based on 10-year risk including participants with eGFR ≥ 120 mL/min/1.73 m^2 generally were smaller than those based on eGFR categories, particularly when adjusted for covariates or when eGFR was modeled as a spline (Table S6).

DISCUSSION

Overall, our results suggest that categorization of kidney function using the CKD-EPI equation more appropriately stratifies middle-aged individuals according to risk of important clinical outcomes compared with the conventional MDRD Study equation. The prevalence of CKD stage 3 (eGFR, 30-59 mL/min/1.73 m^2) at baseline was decreased from 2.5% (n = 347) to 1.4% (n = 196) comparing the CKD-EPI and MDRD Study equations in a large community-based middle-aged population. Importantly, participants who were reclassified upward from CKD stage 3 based on the MDRD Study equation to mildly decreased eGFR (from < 60 to 60-89 mL/min/1.73 m^2) using the CKD-EPI equation had lower risks of all clinical outcomes compared with those who were not reclassified.

Improved risk stratification using categories of $eGFR_{CKD\text{-}EPI}$ is partially a function of inherent properties of the equation: lower risk populations, that is, female, whites, and younger partici-

Table 3. Crude Incidence Rates of Outcomes According to eGFR Categories Determined Using the CKD-EPI and MDRD Study Equations

$eGFR_{MDRD}$ ($mL/min/1.73\ m^2$)	$eGFR_{CKD\text{-}EPI}$ ($mL/min/1.73\ m^2$)					Reclassification (%)
	≥120	90-119	60-89	30-59	<30	
≥120						
No.	716	723	0	0	0	50.2
ESRD	1.5 (0.9-2.4)	0.6 (0.3-1.4)	—	—	—	
All-cause mortality	12.4 (10.5-14.6)	12.7 (10.8-14.9)	—	—	—	
CHD	4.7 (3.6-6.2)	8.7 (7.1-10.6)	—	—	—	
Stroke	4.2 (3.2-5.6)	3.3 (2.4-4.5)	—	—	—	
90-119						
No.	0	5,233	0	0	0	0
ESRD	—	0.4 (0.3-0.6)	—	—	—	
All-cause mortality	—	11.4 (10.7-12.2)	—	—	—	
CHD	—	8.7 (8.1-9.4)	—	—	—	
Stroke	—	3.1 (2.8-3.5)	—	—	—	
60-89						
No.	0	3,079	3,780	0	0	44.9
ESRD	—	0.4 (0.2-0.6)	1.1 (0.8-1.4)	—	—	
All-cause mortality	—	7.4 (6.7-8.2)	12.1 (11.3-13.1)	—	—	
CHD	—	7.5 (6.7-8.3)	10.4 (9.6-11.2)	—	—	
Stroke	—	2.2 (1.8-2.7)	3.6 (3.1-4.1)	—	—	
30-59						
No.	0	0	151	196	0	43.5
ESRD	—	—	1.3 (0.4-4.1)	13.1 (9.3-18.6)	—	
All-cause mortality	—	—	10.0 (6.7-14.9)	32.8 (26.6-40.4)	—	
CHD	—	—	7.7 (4.8-12.2)	21.5 (16.4-28.1)	—	
Stroke	—	—	4.7 (2.6-8.4)	9.4 (6.3-14.0)	—	
<30						
No.	0	0	0	0	27	0
ESRD	—	—	—	—	260.0 (169.5-398.8)	
All-cause mortality	—	—	—	—	150.6 (101.8-222.9)	
CHD	—	—	—	—	44.0 (21.0-92.4)	
Stroke	—	—	—	—	19.2 (6.2-59.6)	

Note: Values expressed as crude incidence rate per 1,000 person-years (95% confidence interval). Conversion factor for eGFR in $mL/min/1.73\ m^2$ to $mL/s/1.73\ m^2$, $\times 0.01667$.

Abbreviations: CHD, coronary heart disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MDRD, Modification of Diet in Renal Disease.

pants,[3,28] are systematically assigned to a higher eGFR category compared with use of the MDRD Study equation. The significantly lower risk for all-cause mortality, CHD, and stroke in persons who were reclassified upward compared with those who were not reclassified was attenuated by the adjustment for age, sex, and race. The coefficients of age, sex, and race in the survival model may compensate for the different age, sex, and race terms in the CKD-EPI and MDRD Study equations. Nevertheless, these findings suggest that the total information content in serum creatinine level and demographics is improved only marginally if one calculates $eGFR_{CKD\text{-}EPI}$ versus $eGFR_{MDRD}$ and uses them in a risk equation along with the same demographics. Risk reclassification improvement based on 10-year risk using the CKD-EPI equation was marginal when adjusted for other risk factors.

The gain using the CKD-EPI equation also was limited when spline terms of eGFR were implemented in the models. Again, it seems that coefficients of multiple spline terms can compensate for differences between the MDRD Study and CKD-EPI equations. Predicted risk using spline models allows for a different risk association across GFRs, limiting differences between eGFR equations that use identical variables. Nevertheless, because clinical decisions and guidelines are based on eGFR categories, the improve-

Table 4. Reclassification of eGFR Categories Using the CKD-EPI and MDRD Study Equations Stratified According to Incident ESRD (yes or no) During Follow-up

	$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)				
	90-119	60-89	30-59	<30	Total No.
Participants who had incident ESRD					
$eGFR_{MDRD}$ (mL/min/1.73 m^2)					
90-119	33	0	0	0	33
60-89	18	63	0	0	81
30-59	0	3	32	0	35
<30	0	0	0	21	21
Total no.	51	66	32	21	170
Participants who did not have incident ESRD					
$eGFR_{MDRD}$ (mL/min/1.73 m^2)					
90-119	5,167	0	0	0	5,167
60-89	3,046	3,700	0	0	6,746
30-59	0	147	164	0	311
<30	0	0	0	6	6
Total no.	8,213	3,847	164	6	12,230

Note: Net reclassification improvement was calculated as follows: clinically correct reclassification (proportion of participants reclassified upward of those did not have ESRD: [3,046 + 147]/12,230) − clinically incorrect reclassification (proportion of participants reclassified upward of those had ESRD: [18 + 3]/170) = 0.138 ($P < 0.001$). Conversion factor for eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MDRD, Modification of Diet in Renal Disease.

ment in risk prediction with eGFR categories is clinically important.

Importantly, for ESRD, an outcome directly linked to decreased eGFR, more accurate risk reclassification based on eGFR categories using the CKD-EPI equation remained statistically significant even after adjustment for demographic variables. Furthermore, it is of note that net reclassification improvement was significantly positive for all outcomes in most subgroups according to age, sex, or race (Table S5). These data indicate that the CKD-EPI GFR estimate is more closely related to risk, classifying a smaller and higher risk subgroup as having CKD stage 3. Thus, in a middle-aged population, CKD-EPI eGFR focuses the attention of clinicians on a subgroup that is more likely to benefit from interventions.

Both the MDRD Study and CKD-EPI equations are limited by the information available for serum creatinine and demographics. Further improvements are likely to require additional markers, such as serum cystatin C level, which improves risk prediction[29] and, when added to creatinine level, GFR estimation.[2] Cystatin C level standardization across methods and laboratories is lagging behind that of serum creatinine level. Thus, it is anticipated that eGFR based on serum creatinine level will continue to be used in most clinical practice settings.[12]

Clinical guidelines recommend that clinical laboratories report eGFR using the MDRD Study equation when serum creatinine measurement is requested.[3,4] About 70% of laboratories currently are reporting eGFR with serum creatinine results.[6] Although false-positive CKD caused by underestimation of GFR using the MDRD Study equation is a concern,[30] the original CKD-EPI and our results suggest the new CKD-EPI equation decreases this false-positive rate.

The present study also raises important interpretative issues about the CKD-EPI equation. In blacks, $eGFR_{CKD-EPI}$ does not differ as much from $eGFR_{MDRD}$ as in whites; consequently, there were lower net reclassification improvements for all outcomes in blacks compared with whites. Most blacks in the study population used to develop the CKD-EPI equation had CKD with decreased GFR.[12] Therefore, the CKD-EPI equation may lack precision in eGFR ≥ 60 mL/min/

1.73 m^2; however, the risk relationship with all outcomes was at least as strong as in whites (data not shown). Further studies are needed to evaluate the accuracy of the CKD-EPI equation in individuals of different race and ethnicity groups with mildly decreased or normal GFRs.

Participants with $eGFR_{CKD\text{-}EPI}$ or $eGFR_{MDRD} \geq$ 120 mL/min/1.73 m^2 had statistically significantly higher risks of all-cause mortality and ESRD. The result for all-cause mortality was not unexpected because high eGFR can result from low serum creatinine level because of muscle wasting secondary to ill health, reflecting inherent limitations of all serum creatinine-based GFR equations.

Why eGFR $\geq$ 120 mL/min/1.73 m^2 using both equations was associated with incident ESRD is unclear. Participants in this category using both equations were likely to be black, have higher body mass index, and have diabetes at baseline compared with the reference group (Table 1; Table S1). These results suggest that the high-eGFR group in this study over-represents diabetic and obese persons with hyperfiltration at risk of progression to CKD. The over-representation of blacks also might contribute to this finding. Blacks have a higher risk of ESRD and are at risk of a more rapid decrease in GFR compared with whites.[31] Persons with eGFR $\geq$ 120 mL/min/1.73 m^2 who had incident ESRD in our study were mostly black (16 of 16 for $eGFR_{CKD\text{-}EPI}$ and 20 of 23 for $eGFR_{MDRD}$).

The reliability of eGFR at high values is another important issue. Individuals, particularly blacks, with measured GFR $\geq$ 120 mL/min/1.73 m^2 were under-represented in the populations from which the CKD-EPI and MDRD Study equations were derived,[7,12] limiting the ability to quantify hyperfiltration and its progression. GFR estimates using both equations have lower precision at higher GFRs.[8,9,12]

Some limitations of the present study should be mentioned. First, because the ARIC Study consists of a middle-aged biethnic community-based population of the United States, additional studies are needed in younger populations, the elderly, or other ethnicities. Second, there were relatively few participants with eGFR of 30-59 mL/min/1.73 m^2, the range in which eGFR alone is used to define CKD and risk relationships become steeper. Finally, albuminuria was not measured at baseline. Thus, we could not evaluate eGFR and albuminuria simultaneously along with other factors that are important for the most accurate risk prediction.

In conclusion, the CKD-EPI equation recently was developed through a large collaborative effort to reduce bias and improve precision and accuracy in estimating measured GFR. The equation uses the same variables (serum creatinine level, age, sex, and race) as the MDRD Study equation, facilitating its implementation in computerized algorithms to estimate GFR in clinical practice and laboratories. This study shows that in a large community-based middle-aged population, the CKD-EPI equation more appropriately classified individuals with respect to risk of ESRD, mortality, CHD, and stroke compared with the MDRD Study equation. This shows that the improved accuracy in estimating GFR using the CKD-EPI equation translated to improved risk prediction and greater clinical utility in middle-aged individuals.

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SUPPLEMENTARY MATERIALS

Table S1: Characteristics of Participants According to Clinical Categories of $eGFR_{MDRD}$

Table S2: Reclassification of eGFR Categories by the CKD-EPI and the MDRD Study Equations, Stratified According to All-Cause Mortality (yes or no) During Follow-up

Table S3: Reclassification of eGFR Categories by the CKD-EPI and MDRD Study Equations, Stratified According to Incident CHD (yes or no) During Follow-up

Table S4: Reclassification of eGFR categories by the CKD-EPI and MDRD Study Equations, Stratified According to Incident Stroke (yes or no) During Follow-up

Table S5: Net Reclassification Improvement by the CKD-EPI Equation Among Participants With eGFR < 120 mL/min/1.73 m^2 by Both Equations

Table S6: Net Reclassification Improvement by the CKD-EPI Equation Based on 10-year Risk Categories (<5%, 5-<10%, 10-<20%, and ≥20%)

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