Risk Implications of the New CKD Epidemiology Collaboration (CKD-EPI) Equation as Compared With the MDRD Study Equation for Estimated GFR: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

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, age, gender and race) as the Modification of Diet in Renal Disease Study (MDRD) equation. Although the CKD-EPI equation estimates GFR more precisely as compared with the MDRD 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 ($\geq$120, 90–119, 60–89, 30–59, <30 ml/min/1.73m^2) by the CKD-EPI and MDRD equations with risk of incident end-stage renal disease (ESRD), all-cause mortality, coronary heart disease (CHD), and stroke.

Results—Median of eGFR$_{CKD-EPI}$ was higher than that of eGFR$_{MDRD}$ (97.6 vs. 88.8 ml/min/1.73m^2, *P*<0.001). The CKD-EPI equation reclassified 44.9% (n=3,079) and 43.5% (n=151) of participants with eGFR$_{MDRD}$ 60–89 and 30–59, respectively, upward to a higher eGFR category but no one with eGFR$_{MDRD}$ 90–119 or <30, lowering the prevalence of CKD stage 3–5 from 2.7% to 1.6%. Participants with eGFR$_{MDRD}$ 30–59 who were reclassified upward had lower risk as compared to those who were not reclassified (ESRD incidence rate ratio, 0.10 [95% CI, 0.03–0.33], all-cause mortality, 0.30 [0.19–0.48], CHD, 0.36 [0.21–0.61], stroke, 0.50 [0.24–1.01]). Similar results were observed for participants with eGFR$_{MDRD}$ 60–89. More frequent reclassification of younger, female, and white participants explained some of these trends. Net reclassification improvement among participants with eGFR <120 was positive for all outcomes (*P*<0.001).

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Limitations—Limited number of cases with eGFR <60 and no measurement of albuminuria.

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

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) utilizing 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 on age, gender, race, and serum creatinine concentration, is most commonly used in clinical practice and epidemiological studies to estimate kidney function. [3−6]

Despite its widespread use, eGFR by the MDRD equation (eGFR$_{MDRD}$) has several limitations. The MDRD equation was developed in a population of individuals with CKD and reduced GFR[7, 8] and systematically underestimates GFR in individuals with measured GFR ≥60 ml/min/1.73m^2.[8−10] Previous studies have suggested that the use of the MDRD equation may result in "over-diagnosis" 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 among individuals with GFR ≥60 ml/min/1.73m^2.[12] The CKD-EPI equation was developed using data from 8,254 individuals from 10 studies including the MDRD study and validated in additional 16 studies containing 3,896 individuals.[12] eGFR by the CKD-EPI equation (eGFR$_{CKD-EPI}$) was more accurate at estimating measured GFR overall and among individuals with normal or mildly reduced kidney function as compared with eGFR$_{MDRD}$. Importantly, the CKD prevalence was reduced from 13.1% based on the MDRD equation to 11.5% by 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 was to evaluate the implications of eGFR categories based on the CKD-EPI equation as compared to those based on the conventional MDRD equation for classifying individuals at risk for 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 four US communities: Forsyth County, North Carolina; suburban Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi. Details of the ARIC Study are described elsewhere.[13] In brief, 15,792 men and women aged 45 to 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 on cardiovascular history (n=1,726), for a final study population size of 13,905 participants. As might be expected, participants who were excluded due to a history of cardiovascular disease (n=1,039) had poorer risk factor profile as compared to the final study population (mean age: 57.0 vs. 54.0 years, systolic blood pressure: 124.1 vs. 121.1 mmHg, and low-density lipoprotein cholesterol [LDL-C]: 147.4 vs. 136.7 mg/dL). Participants who were

excluded due to missing information (n = 801) were similar to the final study population (mean age: 54.2 years, systolic blood pressure: 122.6 mmHg, and LDL-C: 142.7 mg/dL).

Data Collection

ARIC study participants provided information on 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 of $\geq$ 126 mg/dL, non-fasting glucose of $\geq$200 mg/dL, self-reported physician diagnosis of diabetes, or use of oral hypoglycemic medication or insulin. Plasma cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were determined using enzymatic methods, and LDL-C was calculated using the Friedewald equation.[14] Left ventricular hypertrophy by electrocardiogram was defined by the Cornell voltage.[15] Evidence of atherosclerosis of the common carotid arteries (shadowing/plaque on either side) was determined by ultrasound examination.[13, 16]

Estimation of GFR

Serum creatinine concentration was measured using a modified kinetic Jaffe 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 IDMS-traceable 4-variable MDRD Study equation[ND1]: $eGFR_{MDRD} = 175 \times (\text{standardized serum creatinine [mg/dL]})^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$[7, 20] and also using the CKD-EPI equation: $eGFR_{CKD-EPI} = 141 \times (\text{minimum of standardized serum creatinine [mg/dL]}/\kappa \text{ or } 1)^{\alpha} \times (\text{maximum of standardized serum creatinine [mg/dL]}/\kappa \text{ or } 1)^{-1.209} \times 0.993^{age} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$, where κ is 0.7 for female and 0.9 for male and α is -0.329 for female and -0.411 for male.[12] The unique properties of the CKD-EPI equation compared to the MDRD Study equation include a steeper gradient for age, a less steep slope for serum creatinine less than 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-to-white ratio, and a slightly higher female-to-male ratio particularly when a creatinine concentration is less than 0.9 mg/dL.[12] These properties resulted in higher $eGFR_{CKD-EPI}$ as compared to $eGFR_{MDRD}$ particularly in younger population, female, and whites.[12]

Outcome Assessment

ARIC investigators conduct continuous, comprehensive surveillance for all cardiovascular disease-related hospitalizations and deaths in the four communities. All potential cardiovascular events are adjudicated using published criteria.[21–23] We defined incident CHD as a 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 h 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 Disease (ICD) code specified for kidney transplant, dialysis or a procedure indicating dialysis and for individuals with an earlier diagnosis of CKD an 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 (ICD-9 586, 584, 788.9) but without previous CKD were not included.

Statistical Analyses

We categorized eGFR using the following clinically relevant cut-points established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI): ≥120, 90–119, 60–89, 30–59, <30 ml/min/1.73m^2.[3] Participants with eGFR <15 ml/min/1.73m^2 (CKD stage 5) were not considered separately in the present study, as there were few participants in this category (n=16 for eGFR$_{CKD-EPI}$ and n=15 for eGFR$_{MDRD}$). Individuals with eGFR ≥120 ml/min/1.73m^2 were considered separately from those with eGFR 90–119 ml/min/1.73m^2 under the assumption that high eGFR may result from very low creatinine due to 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 by both equations and the 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, gender, and race. We also evaluated the risk of clinical outcomes according to categories of eGFR, using eGFR of 90–119 ml/min/1.73m^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 the above 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 the eGFR$_{CKD-EPI}$ categories, calculated the proportion of participants reclassified by eGFR$_{CKD-EPI}$ 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[ND2],[26] calculated as the sum of the proportion of participants reclassified downward to a lower eGFR category among individuals with an outcome and the proportion of participants reclassified upward to a higher eGFR category among individuals without an outcome, less the sum of the proportion of participants reclassified upward among individuals with an outcome and the proportion of participants reclassified downward among individuals without an outcome. This calculation represents the sum of the two terms corresponding to "clinically correct" reclassification, less the two terms reflecting "clinically incorrect" reclassification. In sensitivity analyses, we also assessed net reclassification improvement using 10-year risk categories (<5%, 5-<10%, 10-<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 a *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of Study Participants

Participants with CKD stage 3 (eGFR$_{CKD-EPI}$ of 30–59 ml/min/1.73m^2) or stage 4/5 (eGFR$_{CKD-EPI}$ <30 ml/min/1.73m^2) were more likely to be older, female, and black and have more comorbidities including diabetes as compared to individuals with eGFR$_{CKD-EPI}$ of 90–119 ml/min/1.73m^2 (Table 1). The category of eGFR$_{CKD-EPI}$ ≥120 ml/min/1.73m^2 mainly consisted of black females who also tended to have higher prevalence of diabetes and left ventricular hypertrophy, more often reported taking anti-hypertensive medications, and have higher body mass index compared to those with eGFR$_{CKD-EPI}$ of 90–119 ml/min/1.73m^2. The mean age in this group, however, was lower compared to 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$_{CKD-EPI}$ was higher among persons with eGFR of 30–89 ml/min/1.73m^2 but lower than eGFR$_{MDRD}$ among individuals with eGFR ≥120 ml/min/1.73m^2 (Table 1 and Figure 1). Mean eGFR$_{CKD-EPI}$ and eGFR$_{MDRD}$ were similar for categories of eGFR 90–119 and less than 30 ml/min/1.73m^2. Overall, the median (interquartile range) of eGFR$_{CKD-EPI}$ was higher than that of eGFR$_{MDRD}$ (97.6 [87.3–105.6] and 88.8 [79.8–102.1] ml/min/1.73m^2, respectively, $P<0.001$). In particular, median eGFR$_{CKD-EPI}$ was higher than eGFR$_{MDRD}$ among female, whites, and younger individuals (+8.8 ml/min/1.73m^2 in female vs. +6.9 in male, +10.0 in whites vs. +5.8 in blacks, and +9.5 in younger [45–54 y] vs. +7.3 in older [55–64 y]) as expected. The distribution of eGFR$_{CKD-EPI}$ and eGFR$_{MDRD}$ are shown in Panel A of Figure 2.

Incidence Rates According to eGFR by Each Equation

During median follow-up of 16.9 years, there were 192 cases of ESRD, 2,455 deaths, 1,850 cases of CHD, and 648 cases of stroke. The continuous relationships between eGFR by both equations and incidence rates of the clinical outcomes with and without adjusting for age, gender and race are shown in Figure 2. Although the trends for both equations were quite similar, incidence rates of the four outcomes were higher throughout the range of moderately decreased GFR$_{CKD-EPI}$ as compared with the same levels of eGFR$_{MDRD}$. The positive slopes of eGFR with ESRD, all-cause mortality, and stroke at a range of eGFR >105 ml/min/1.73m^2 were steeper for GFR$_{CKD-EPI}$ than eGFR$_{MDRD}$. In contrast, CHD risk was lower even at eGFRs above 120 ml/min/1.73m^2 for eGFR$_{CKD-EPI}$ but not for eGFR$_{MDRD}$.

The adjusted incidence rate ratios for each outcome comparing eGFR categories of the CKD-EPI and MDRD equations are presented in Table 2. For both equations, the categories of eGFR <60 ml/min/1.73m^2 were consistently associated with similarly greater risks of each of the outcomes. Individuals with eGFR 60–89 ml/min/1.73m^2 by either equation had higher risks of incident ESRD and stroke as compared with the reference groups. The incidence rates of ESRD and all-cause mortality among participants with eGFR ≥120 ml/min/1.73m^2 by both equations were significantly higher as compared to the reference groups for both equations. Harrell's C-statistics were obtained after Cox proportional hazards models with covariates used 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 the 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 90–119 changed dramatically from 4,830 by the MDRD Study equation to 8,357 with the CKD-EPI equation. However, the risk of these groups is similar since the absolute risk of individuals with eGFR$_{CKD-EPI}$ 90–119 but eGFR$_{MDRD}$ 60–89 or ≥120 is very similar with individuals with eGFR 90–119 by both equations (Table 3).

Cross-Tabulated Incidence Rates According to eGFR by Both Equations

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

Importantly, participants who were reclassified upward to a higher eGFR category consistently had lower risk of all outcomes than those who remained unchanged in the same eGFR category. For participants with $eGFR_{MDRD}$ 30–59 who were reclassified to $eGFR_{CKD-EPI}$ of 60–89, the incidence rate ratios compared to those who stayed in the lower category was: 0.10 (95% CI, 0.03 to 0.33) for ESRD (1.3 vs. 13.1 per 1000 person years in Table 3), 0.30 (0.19 to 0.48) for all-cause mortality, 0.36 (0.21 to 0.61) for CHD and 0.50 (0.24 to 1.01) for stroke. Similar results were observed for participants with $eGFR_{MDRD}$ 60–89 (ESRD incidence rate ratio, 0.35 [95% CI, 0.20–0.58], all-cause mortality, 0.61 [0.54–0.69], CHD, 0.72 [0.63–0.82], stroke, 0.62 [0.49–0.78]). The pattern was less consistent for participants with $eGFR_{MDRD}$ ≥120 ml/min/1.73m^2 who were reclassified downward to $eGFR_{CKD-EPI}$ of 90–119.

Subsequently, we compared age-, gender-, and race-adjusted incidence rates and found that participants reclassified upward by the CKD-EPI equation still tended to have lower risk as compared to those who were not reclassified, although this comparison was only statistically significant for ESRD (ESRD incidence rate ratio, 0.55 [95% CI, 0.31–0.95] in $eGFR_{MDRD}$ of 60–89 ml/min/1.73m^2 and 0.13 [0.04–0.47] in $eGFR_{MDRD}$ of 30–59 ml/min/1.73m^2; all-cause mortality, 0.94 [0.82–1.08] and 0.72 [0.42–1.23]; CHD, 0.94 [0.82–1.08] and 0.78 [0.41–1.47]; stroke, 0.95 [0.74–1.21] and 0.95 [0.40–2.23], respectively).

Net Reclassification Improvement

The analysis of net reclassification improvement based on eGFR categories was conducted after excluding participants with either $eGFR_{CKD-EPI}$ or $eGFR_{MDRD}$ ≥120 ml/min/1.73m^2, since re-classification to lower values from this group has a different meaning due to the J-shaped associations of eGFR with risk. The detailed table for calculating net reclassification improvement for incident ESRD is shown in Table 4 (Tables S2 to 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 by the CKD-EPI equation. On the other hand, among 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 by 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, gender, and age (45–54 or 55–64 y), though 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 were generally smaller than those based on eGFR categories, particularly when adjusted for covariates or where 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 as compared to the conventional MDRD Study equation. The prevalence of CKD stage 3 (eGFR 30–59 ml/min/1.73m^2) at baseline was reduced from 2.5% (n=347) to 1.4% (n=196) when 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 reduced eGFR (from <60 to 60–89 ml/min/1.73m^2) by the CKD-EPI equation had lower risks of all clinical outcomes as compared to those who were not reclassified.

Improved risk stratification using categories of $eGFR_{CKD-EPI}$ is partially a function of inherent properties of the equation: lower risk populations, i.e., female, whites, and younger,[3, 28] are systematically assigned to a higher eGFR category as compared to use of the MDRD Study

equation. Indeed, the significantly lower risk for all-cause mortality, CHD, and stroke among persons who were reclassified upward as compared with those who were not reclassified was attenuated by the adjustment for age, gender, and race. The coefficients of age, gender, and race in the survival model may compensate for the different age, gender, and race terms in the CKD-EPI and MDRD study equations. Nevertheless, these findings suggest that the total information content in serum creatinine and demographics is only marginally improved if one calculates the $eGFR_{CKD-EPI}$ vs. $eGFR_{MDRD}$ and uses them in a risk equation along with the same demographics. Indeed, risk reclassification improvement based on 10-year risk by the CKD-EPI equation was marginal when adjusted for other risk factors.

The gain by the CKD-EPI equation was also 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 and CKD-EPI study equations. Predicted risk by spline models allows for a different risk association across GFR, limiting differences between eGFR equations which use identical variables. Nevertheless, since clinical decisions and guidelines are based on eGFR categories, the improvement 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 by the CKD-EPI equation remained statistically significant even after the 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, gender, 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 and CKD-EPI study equations are limited by the information available in serum creatinine and demographics. Further improvements are likely to require additional markers such as serum cystatin C, which improves risk prediction[29] and, when added to creatinine, GFR estimation.[2] Cystatin C standardization across methods and laboratories is lagging that of serum creatinine. Thus, it is anticipated that eGFR based on serum creatinine will continue to be used in most clinical practice settings.[12]

Clinical guidelines recommend that clinical laboratories should report eGFR using the MDRD Study equation whenever serum creatinine measurement is requested.[3, 4] Indeed, about 70% of laboratories are currently reporting eGFR along with serum creatinine results.[6] Although false-positive CKD due to underestimation of GFR by the MDRD Study equation is a concern, [30] the original CKD-EPI and our results suggest the new CKD-EPI equation reduce 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 and, consequently, there were lower net reclassification improvements for all outcomes in blacks as compared to whites. The majority of blacks in the study population used to develop the CKD-EPI equation had CKD with reduced GFR.[12] Therefore, the CKD-EPI equation may lack precision in GFR estimation ≥ 60 ml/min/1.73m^2 but 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 among individuals of different race and ethnicity groups with mildly decreased or normal GFR levels.

Participants with $eGFR_{CKD-EPI}$ or $eGFR_{MDRD} \geq 120$ ml/min/1.73m^2 had statistically significantly higher risks for all-cause mortality and ESRD. The result for all-cause mortality was not unexpected, as high eGFR can result from low serum creatinine due to muscle wasting

secondary to ill health, reflecting inherent limitations of all serum creatinine-based GFR equations.

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

Reliability of eGFR at high values is another important issue. Individuals, particularly blacks, with measured GFR $\geq$120 ml/min/1.73m^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. Indeed, GFR estimates by both equations have lower precision at higher GFRs.[8, 9, 12]

Some limitations of the present study should be mentioned. First, since the ARIC study consists of a middle-aged, bi-ethnic community-based population of the US, 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/1.73m^2, the range where 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 which are important for the most accurate risk prediction.

In conclusion, the CKD-EPI equation was recently 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, age, gender 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-age population the CKD-EPI equation more appropriately classified individuals with respect to risk of ESRD, mortality, CHD and stroke as compared to the MDRD Study equation. This demonstrates that the improved accuracy in estimating GFR by the CKD-EPI equation translated to improved risk prediction and greater clinical utility among middle-aged individuals.

Descriptive Text for Online Delivery

Hyperlink: Supplementary Table S1

About: Characteristics of Participants According to Clinical Categories of eGFR$_{MDRD}$

Hyperlink: Supplementary Table S2

About: 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

Hyperlink: Supplementary Table S3

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

Hyperlink: Supplementary Table S4

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

Hyperlink: Supplementary Table S5

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

Hyperlink: Supplementary Table S6

About: Net Reclassification Improvement by the CKD-EPI Equation based on 10-year risk categories (<5%, 5-<10%, 10-<20%, and≥20%)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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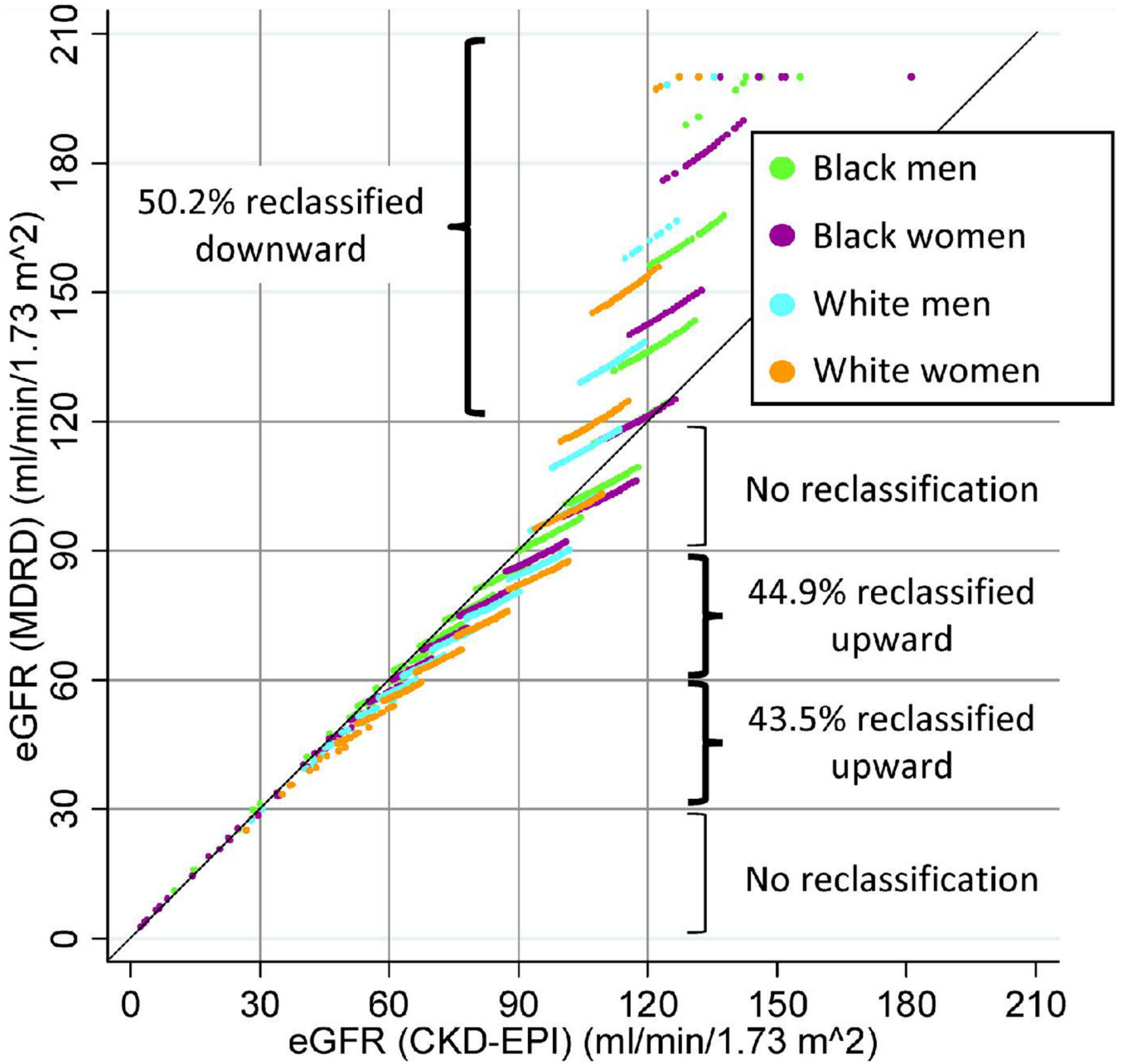
Figure 1.
Scatter plot of eGFR$_{CKD-EPI}$ and eGFR$_{MDRD}$ according to the combination of gender and race. Points in off-diagonal boxes indicate individuals who are reclassified into a higher (below the diagnonal) or lower (above the diagonal) eGFR category by eGFR$_{CKD-EPI}$ compared to eGFR$_{MDRD}$. The graph includes 13,905 individuals but points with the same eGFR plot on top of each other. Individuals with eGFR$_{MDRD}$ >200 are plotted at 200.
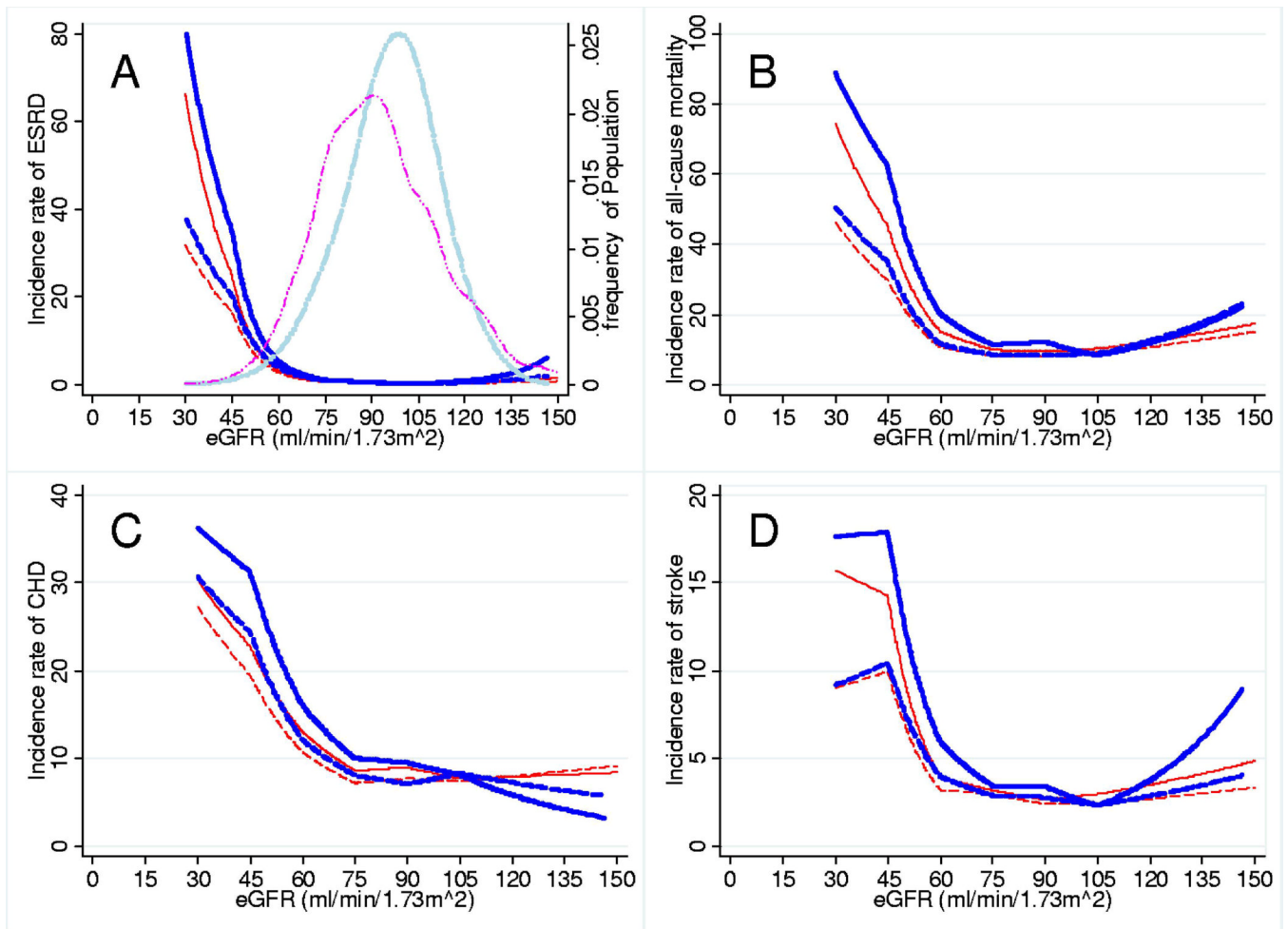
Figure 2.
Incidence Rates (per 1,000 person-years) of Outcomes according to eGFR by the CKD-EPI and MDRD study equations. Incidence rates of (A) ESRD, (B) all-cause mortality, (C) CHD, and (D) stroke and eGFR (ml/min/1.73m^2) by the CKD-EPI equation (blue and thick) and the MDRD equation (red) without (solid lines) and with (dash lines) adjustment for mean values of age, gender, and race. The long-dash two dots lines in the panel A demonstrate kernel density plots of the distributions of eGFR$_{CKD-EPI}$ (light blue and thick) and eGFR$_{MDRD}$ (magenta).

Table 1

Characteristics of Participants according to Clinical Categories of eGFR_{CKD-EPI}

Characteristic	Categories of eGFR$_{CKD-EPI}$ (ml/min/1.73m^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 (n = 13,883)					
<12 yr	253 (35)	2,003 (22)	798 (20)	68 (35)	16 (59)
12 to 16 yr	224 (31)	3,771 (42)	1,620 (41)	69 (35)	9 (33)
>16 yr	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)
BMI (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 BP (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 BP (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
LDL-C (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
HDL-C (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$_{CKD-EPI}$ (ml/min/1.73m^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/1.73m^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 ± SD or number (percent). Conversion factors for units: LDL-C and HDL-C 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/1.73m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations and definitions: eGFR_{CKD-EPI}, estimated glomerular filtration rate (eGFR) calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation; eGFR_{MDRD}, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease (MDRD) Study equation; BP, blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease

Table 2

Adjusted Incidence Rate Ratio (95% CI) for Outcomes according to eGFR Categories Determined by Either CKD-EPI or MDRD Study Equation

	Categories of eGFR, ml/min/1.73m²				
	>=120	90–119	60–89	30–59	<30
No. Participants					
CKD-EPI*	641	8,357	3,645	171	21
MDRD*	1,297	4,830	6,380	307	21
Outcomes					
ESRD					
CKD-EPI	2.07 (1.13–3.79)	(ref)	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)	(ref)	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)	(ref)	1.01 (0.91–1.11)	1.69 (1.33–2.15)	5.53 (3.48–8.80)
MDRD	1.27 (1.10–1.49)	(ref)	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)	(ref)	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)	(ref)	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)	(ref)	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)	(ref)	1.16 (0.97–1.38)	1.88 (1.29–2.75)	1.81 (0.57–5.76)

Note: Adjusted for following covariates: age, race, gender, level of education, systolic blood pressure, antihypertensive medication, diabetes, smoking, body mass index, low- and high -density lipoprotein cholesterol, left ventricular hypertrophy, and carotid atherosclerosis.

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

*
Participants included in the fully adjusted analysis.

Table 3

Crude Incidence Rates (95% CIs) (per 1,000 Person-Years) of Outcomes according to eGFR Categories Determined by CKD-EPI and MDRD Study Equations

eGFR$_{MDRD}$, ml/min/1.73m²	eGFR$_{CKD-EPI}$, ml/min/1.73m²					
	>=120	90–119	60–89	30–59	<30	reclassification
>=120						
n	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						
n	0	5,233	0	0	0	0%
ESRD	-	0.4 (0.3 to 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						
n	0	3,079	3,780	0	0	44.9%
ESRD	-	0.4 (0.2 to 0.6)	1.1 (0.8 to 1.4)	-	-	
All-cause mortality	-	7.4 (6.7 to 8.2)	12.1 (11.3 to 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						

eGFR$_{MDRD}$, ml/min/1.73m^2	eGFR$_{CKD-EPI}$, ml/min/1.73m^2					reclassification
	>=120	90–119	60–89	30–59	<30	
n	0	0	151	196	0	43.5%
ESRD	-	-	1.3 (0.4 to 4.1)	13.1 (9.3 to 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						
n	0	0	0	0	27	0%
ESRD	-	-	-	-	260.0 (169.5–398.8)	
All-cause mortality	-	-	-	-	150.6 (101.8 to 222.9)	
CHD	-	-	-	-	44.0 (21.0–92.4)	
Stroke	-	-	-	-	19.2 (6.2–59.6)	

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

Conversion factor for eGFR in ml/min/1.73m^2 to mL/s/1.73 m^2, ×0.01667.

Table 4

Reclassification of eGFR Categories by the CKD-EPI and the MDRD Study Equations, Stratified according to Incident ESRD (yes or no) during the Follow-Up

	eGFR_CKD-EPI, ml/min/1.73m²				
	90–119	60–89	30–59	<30	Total no.
Participants who had incident ESRD					
eGFR_MDRD, ml/min/1.73m²					
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/1.73m²					
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 (NRI) was calculated as follows: clinically correct reclassification (proportion of participats reclassified upward among those did not have ESRD: [3,046 + 147]/12,230) - clinically incorrect reclassification (proportion of participats reclassified upward among those who had ESRD: [18 + 3]/170) = 0.138 (*P*<0.001)

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

Conversion factor for eGFR in ml/min/1.73m² to mL/s/1.73 m², ×0.01667.