Comparison of risk prediction using the CKD-EPI equation and the MDRD Study equation for estimated glomerular filtration rate

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Abstract

Context—The CKD-EPI equation more accurately estimates glomerular filtration rate (eGFR) than the MDRD Study equation using the same variables, especially at higher GFR, but definitive evidence of its risk implications in diverse settings is lacking.

Objective—To evaluate risk implications of eGFR_{CKD-EPI} compared to eGFR_{MDRD} in populations with a broad range of demographic and clinical characteristics.

Design, Setting, and Participants—Meta-analyses based on data from 1,130,472 adults (aged 18 years or older) from 25 general population, 7 high-risk (of vascular disease), and 13 chronic kidney disease (CKD) cohorts. Data transfer and analyses were conducted between March 2011 and March 2012.

Main Outcome Measures—All-cause mortality (84,482 deaths from 40 cohorts), cardiovascular mortality (22,176 events from 28 cohorts), and end-stage renal disease (ESRD) (7,644 events from 21 cohorts) during 9.4 million person-years of follow-up (median of mean follow-up time across cohorts was 7.4 years).
Results—eGFR was classified into six categories (≥90, 60-89, 45-59, 30-44, 15-29, and <15 ml/min/1.73m²) by both equations. Compared to eGFR_{MDRD}, 24.4% and 0.6% of participants from general population cohorts were reclassified to a higher and lower eGFR category by the CKD-EPI equation, respectively, and the prevalence of CKD stage 3-5 (eGFR <60 ml/min/1.73m²) was reduced from 8.7% to 6.3%. 34.7% of participants with eGFR_{MDRD} 45-59 were reclassified to eGFR_{CKD-EPI} 60-89 and had lower incidence rates (per 1,000 person-years) of outcomes compared to those not reclassified (9.9 vs. 34.5 for all-cause mortality, 2.7 vs. 13.0 for cardiovascular mortality, and 0.5 vs. 0.8 for ESRD). The corresponding adjusted hazard ratios were 0.80 (95% confidence interval, 0.74 to 0.86) for all-cause mortality, 0.73 (0.65 to 0.82) for cardiovascular mortality, and 0.49 (0.27 to 0.88) for ESRD. Similar findings were observed in other eGFR_{MDRD} categories. Net reclassification improvement (NRI) based on eGFR categories was significantly positive for all outcomes (range from 0.06 to 0.13, all P<0.001). NRI was similarly positive in most subgroups defined by age (< and ≥65 years), sex, race/ethnicity (white, Asian, and black), and presence or absence of diabetes and hypertension. The results in high-risk and CKD cohorts were largely consistent with the general population cohorts.

Conclusions—The CKD-EPI equation classified fewer individuals as CKD and more accurately categorized the risk for mortality and ESRD than did the MDRD Study equation across a broad range of populations.

Glomerular filtration rate (GFR) is used in the diagnosis of chronic kidney disease (CKD) and is an independent predictor of all-cause and cardiovascular mortality and kidney failure in a wide range of populations. Clinical guidelines recommend reporting estimated GFR (eGFR) when serum creatinine is measured, and, currently, 84% of US laboratories report eGFR. Although the Modification of Diet in Renal Disease (MDRD) Study equation is recommended for estimating GFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) has recently proposed an alternative equation, which applies different coefficients to the same four variables used in the MDRD Study equation (age, sex, race, and serum creatinine). The new CKD-EPI equation estimates measured GFR more accurately than the MDRD Study equation in most, but not all, studies. However, only 4% of US laboratories reporting eGFR used the CKD-EPI equation in June 2011; 92% of laboratories still used the MDRD Study equation and 4% used other equations. A few studies suggest that the better estimation of GFR by the CKD-EPI equation is reflected in better clinical risk prediction than the MDRD Study equation. However, these studies include predominantly white people with higher levels of kidney function. Also, implications of the CKD-EPI equation in the elderly have yet to be elucidated. The objective of this collaborative study was to comprehensively evaluate whether eGFR computed by the CKD-EPI equation predicts risk for adverse outcomes more accurately than the MDRD Study equation in a broad range of populations. Such information will help clinicians, laboratories and policy makers decide whether eGFR reporting should be based on the MDRD Study or the CKD-EPI equation.

METHODS

Study Design

Details of the Chronic Kidney Disease Prognosis Consortium (CKD-PC) were described previously. To be included in the consortium, a study had to have at least 1,000 participants (not applied to studies only enrolling CKD patients [CKD cohorts]), information on baseline eGFR and urine albumin levels, and a minimum of 50 events for any of the outcomes of interest. As recommended, we preferentially selected urine albumin-to-creatinine ratio (ACR) as the measure of albuminuria. However, we also
accepted urine albumin excretion and urine protein-to-creatinine ratio (PCR) as well as a qualitative measurement using dipstick.¹ This analysis consists of data from 45 cohorts (25 general population cohorts, seven high-risk cohorts with participants selected for cardiovascular or kidney disease risk factors, and 13 CKD cohorts). Data transfer (from collaborating cohorts to the CKD-PC Data Coordinating Center) and analyses for the present study were conducted between March 2011 and March 2012. This study is based on secondary data analysis of pre-existing, de-identified/de-linked dataset, and was approved by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health. Information about ethical review of individual studies is available in the publications of the constituent cohorts.²¹,²⁴,²⁷-⁶⁹

Estimation of GFR

We calculated eGFR from serum creatinine standardized to isotope dilution mass spectrometry (IDMS) using the MDRD Study equation⁹ and the CKD-EPI equation.¹⁰ For studies in which creatinine measurement was not standardized to IDMS, we reduced the creatinine levels by 5%, the calibration factor used to adjust non-standardized MDRD Study samples to IDMS.⁷⁰

Covariates

Diabetes mellitus was defined as fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L, hemoglobin A1c ≥6.5%, use of glucose lowering drugs, or self-reported diabetes. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol ≥5.0 mmol/L in people with prior cardiovascular disease (CVD) and as ≥6.0 mmol/L otherwise or use of lipid lowering drugs. CVD history was defined as a history of myocardial infarction, coronary revascularization, heart failure or stroke. Smoking was dichotomized as current versus former/non-smokers. Race/ethnicity was categorized as white, Asian, black, Hispanic, and others.

Outcomes

The outcomes of interest were all-cause mortality, cardiovascular mortality, and end-stage renal disease (ESRD). Cardiovascular mortality was defined as death due to myocardial infarction, heart failure, sudden cardiac death, or stroke. ESRD was defined as start of renal replacement therapy or death due to kidney disease other than acute kidney injury.

Statistical Analyses

Statistics were first obtained within each study and then were meta-analyzed across studies by a random-effects model. Analyses were restricted to subjects aged 18 years or older. Any subject with missing values for eGFR or albuminuria at baseline was excluded. Missing values for all other covariates were estimated by mean imputation. The analysis overview and analytic notes for individual studies are described in eAppendix 2. Heterogeneity was quantified using the I² test for heterogeneity and the F statistic. We conducted meta-regression analysis with a random-effects model to explore sources of heterogeneity. General population, high-risk and CKD cohorts were meta-analyzed separately.

We evaluated the eGFR distribution and eGFR-risk relationship for the two equations separately. Cox proportional hazards models were fitted with eGFR linear splines (knots at 30, 45, 60, 75, 90, and 105 [this knot was not applied to CKD cohorts] ml/min/1.73 m²). All Cox models adjusted for age, sex, race/ethnicity (blacks vs. non-blacks), smoking, history of CVD, systolic blood pressure (continuous), diabetes, serum total cholesterol concentration (continuous), body mass index (continuous), and albuminuria (log-transformed ACR and
PCR as continuous variables or dipstick as a categorical variable [negative, trace, 1+, 2+, and ≥3+]. From these models, hazard ratio was computed for each 1 ml/min/1.73 m$^2$ of eGFR from 15 to 120 with a reference point at 95 ml/min/1.73 m$^2$ (50 ml/min/1.73 m$^2$ for CKD cohorts). Model discrimination was assessed using a c-statistic which allows for censoring.\textsuperscript{71}

We cross-tabulated eGFR using clinically relevant categories (≥90, 60-89, 45-59, 30-44, 15-29, <15 ml/min/1.73 m$^2$)\textsuperscript{1,2} and evaluated the proportion of participants in each category of eGFR\textsubscript{MDRD} that was reclassified by eGFR\textsubscript{CKD-EPI}. To evaluate factors associated with reclassification, baseline characteristics of participants in each study were compared according to the reclassification status by the CKD-EPI equation (reclassified upward to a higher eGFR category, not reclassified, or reclassified downward to a lower eGFR category). Since there were few participants with eGFR <15 ml/min/1.73 m$^2$ in the general population (<0.1%) and high-risk (0.2%) cohorts, we only reported results for this eGFR category in the CKD cohorts.

Given that GFR category is a central measure for defining, staging and managing CKD (including indications for referral),\textsuperscript{1,2} we \textit{a priori} designated the impact of reclassification in clinical eGFR categories as the primary analysis.\textsuperscript{21-23} We assessed risk of clinical outcomes among participants who were reclassified for eGFR categories compared with those who were not reclassified. Overall improvement in reclassification based on clinical eGFR categories was assessed applying net reclassification improvement (NRI).\textsuperscript{21,72} To assess generalizability, we calculated NRI in subgroups according to age (<65 and ≥65 years old), sex, race/ethnicity (white, Asian, and black), and presence or absence of diabetes and hypertension. Due to sparse data, we could not reliably investigate Hispanics and other racial/ethnic groups. NRI was also estimated in subgroups according to albuminuria levels. All analyses were conducted using Stata/MP 11.2 software (www.stata.com) and a $P$-value of less than 0.05 was considered statistically significant.

**RESULTS**

**Study Characteristics**

Participants from 45 cohorts were from 40 countries/regions of Asia, Europe, North and South America, Middle East and Oceania. Baseline characteristics of each cohort are shown in eTable 1. Overall, 1,130,472 adults (940,366 from general population, 151,494 from high-risk, and 38,612 from CKD cohorts) were followed for 9,415,863 person-years (the median of mean follow-up time across collaborating cohorts was 7.4 years [interquartile range, 4.2 to 10.5 years]). Forty cohorts reported on 84,482 deaths (61,770 from general population, 13,693 from high-risk, and 9,019 from CKD cohorts); 28 cohorts reported on 22,176 CVD deaths (17,009 from general population, 4,271 from high-risk, and 896 from CKD cohorts); and 21 cohorts reported on 7,644 ESRD events (730 from general population, 954 from high-risk, and 5,960 from CKD cohorts).

**Distribution and Relative Risk according to eGFR by each Equation**

Mean eGFR was higher computed by the CKD-EPI equation than the MDRD Study equation in the general population (88.9 vs. 81.5 ml/min/1.73 m$^2$, FIGURE 1A) and the high-risk (84.6 vs. 80.6 ml/min/1.73 m$^2$, eFigure 1A) cohorts but was comparable in the CKD cohorts (41.4 vs. 40.6 ml/min/1.73 m$^2$) (eFigure 2A). The shift of distribution toward higher eGFR by the CKD-EPI equation was more evident in younger people (<65 years), female, and non-blacks (eFigures 3-5). Accordingly, the prevalence of CKD stages 3 to 5 (<60 ml/min/1.73 m$^2$) was lower by the CKD-EPI equation than the MDRD Study equation in the general population (6.3% vs. 8.7%) and high-risk (14.6% vs. 17.7%) cohorts. The
lower prevalence of CKD stages 3 to 5 by the CKD-EPI equation was observed in most of the individual cohorts with a small increase in only two cohorts of elderly subjects\textsuperscript{30,39}(eFigure 6).

The pattern of the eGFR-risk relationship was similar for both equations in the general population cohorts after adjusting for potential confounders (Figure 1B-D). However, the adjusted hazard ratio of lower eGFR compared with eGFR of 95 ml/min/1.73 m\textsuperscript{2} became significant at a higher level for eGFR\textsubscript{CKD-EPI} than for eGFR\textsubscript{MDRD}, particularly for cardiovascular mortality (77 vs. 68 ml/min/1.73 m\textsuperscript{2}) and ESRD (82 vs. 70 ml/min/1.73 m\textsuperscript{2}). Within the range of eGFR <45 ml/min/1.73 m\textsuperscript{2}, the hazard ratios were largely comparable between both equations for the mortality outcomes. The steeper risk gradient along with low eGFR was more evident in unadjusted analysis for mortality (eFigure 7). The higher risk of all-cause and cardiovascular mortality in the higher eGFR range (105-120 ml/min/1.73 m\textsuperscript{2}) was more pronounced for the CKD-EPI equation than the MDRD Study equation. This effect was not observed in unadjusted analysis. Similar eGFR-risk relationships were observed in the high-risk and CKD cohorts (eFigures 1B-D and 2B-D), but the higher risk at higher levels of eGFR was not evident. Using these models with eGFR splines, traditional risk factors, and albuminuria, c-statistics, which focus on ranking alone and ignore absolute levels and categories,\textsuperscript{73} were almost identical for the CKD-EPI and MDRD Study equations in all three types of cohort (0.783 [0.758 to 0.807] vs. 0.783 [0.759 to 0.808] for all-cause mortality, 0.835 [0.800 to 0.869] vs. 0.835 [0.801 to 0.869] for cardiovascular mortality and 0.920 [0.888 to 0.953] vs. 0.919 [0.885 to 0.952] for ESRD in the general population cohorts, respectively) (eTable 2).

**eGFR Category Reclassification and its Risk Implications**

In the general population cohorts, 25.0% of participants were reclassified by the CKD-EPI equation (24.4% to a higher eGFR category and 0.6% to a lower eGFR category) (FIGURE 2). Most reclassification occurred among participants with eGFR\textsubscript{MDRD} between 45-89 ml/min/1.73 m\textsuperscript{2}. A similar reclassification pattern was observed in the high-risk cohorts, although there was less reclassification (15.4% upward and 1.2% downward, eFigure 8). In the CKD cohorts, we observed much less upward reclassification (6.6%) but slightly more downward reclassification (3.2%) by the CKD-EPI equation (Figure 9).

Participants who were reclassified upward to a higher eGFR category by the CKD-EPI equation were more likely to be younger, female, and non-black, and, thus, to have fewer comorbid conditions such as hypertension, diabetes, and clinically significant albuminuria as compared to individuals who remained in the same eGFR category (Table 1 and eTable 3). In contrast, the participants reclassified downward to a lower eGFR category by the CKD-EPI equation were much older than those who were not reclassified in most studies (mean age in general population cohorts, 77 years vs. 49 years). Blacks tended to be reclassified less frequently (in either direction) in the general population cohorts but, at lower GFR range (CKD cohorts), were reclassified downward more frequently as compared to non-blacks.

Participants in general population cohorts who were reclassified upward and downward by the CKD-EPI equation had consistently lower and higher incidence rates for all outcomes, respectively, than those who remained in the same eGFR category (Table 2). This association remained the same even after adjustment for potential confounders, with only a few exceptions (none of which were significant). When we focused on clinically important upward reclassification from CKD stage 3a (eGFR 45-59 ml/min/1.73 m\textsuperscript{2}) to mildly reduced eGFR (60-89 ml/min/1.73 m\textsuperscript{2}), this reclassification was associated with lower incidence rates compared to no reclassification (incidence rate per 1,000 person-years, 9.9 vs. 34.5 [difference, −24.6] for all-cause mortality, 2.7 vs. 13.0 [−10.3] for cardiovascular mortality,
and 0.5 vs. 0.8 [-0.3] for ESRD). Of note, this reclassification was associated with 20-51% lower risk of these outcomes even after the adjustment for traditional risk factors and albuminuria. We obtained similar results for the groups below and above age 65 years (eTables 4 and 5). Among the statistically significant reclassifications in Table 2, heterogeneity across studies was minimal to moderate ($I^2=0.0-52.5\%$, $P$-values range from 0.82 to 0.006). Similar findings were observed in the high-risk (eTable 6) and CKD cohorts (eTable 7). For ESRD, analysis with mortality as a competing risk provided similar findings (eTable 8).

In the general population cohorts, NRI was significantly positive (favoring the CKD-EPI equation) for all outcomes (0.11 [95% CI, 0.09-0.13] for all-cause mortality, 0.13 [0.09-0.16] for cardiovascular mortality, and 0.06 [0.02-0.10] for ESRD) (FIGURE 3). There was high heterogeneity between individual cohorts for overall NRI ($I^2=71\%$ to 97%, all $P<0.01$). However, this heterogeneity reflected quantitative rather than qualitative differences, since the CKD-EPI equation was favored in almost all general population studies (eFigures 10-12). We conducted meta-regression analysis with covariates (eTable 9). Studies with higher mean age and prevalence of diabetes tended to have lower NRI for cardiovascular mortality (eFigures 13 and 14). NRI for other associations did not vary significantly across studies.

NRI was positive in most of the subgroups according to age, sex, race/ethnicity and presence or absence of diabetes and hypertension (FIGURE 3). NRI was comparable between females and males and between ages <65 years and ≥65 years except for a lower NRI in age ≥65 years for ESRD. NRI was positive even in the age category of ≥75 years for all-cause mortality (0.03 [95% CI, 0.02 to 0.05]) and cardiovascular mortality (0.02 [0.01 to 0.03]). NRI was negative but not significant for ESRD (−0.04 [−0.10 to 0.02], $P=0.149$). NRI for mortality outcomes was lower in blacks as compared to whites and Asians but still significantly favored the CKD-EPI equation. With further stratification by the combination of these demographic variables, NRI was positive (favoring the CKD-EPI equation) in 33 out of 36 comparisons and was statistically significant in 17 comparisons (eTable 10). None of three negative NRIs (favoring the MDRD Study equation) were significant. Similarly, NRI was positive in most subgroups in the high-risk and CKD cohorts (eFigures 15 and 16 and eTables 11 and 12). NRI was also positive in most subgroups defined according to albuminuria level (eTable 13).

**COMMENT**

In our data from more than 1 million participants residing in 40 countries/regions, approximately one quarter of participants were reclassified to a higher eGFR category by the CKD-EPI equation compared to the MDRD Study equation (24.4% in the general population, 15.4% in high-risk, and 6.6% in CKD cohorts), lowering the prevalence of CKD in all cohorts except for the elderly. Participants who were reclassified upward had lower risks of mortality and ESRD as compared to those not reclassified even after adjusting for age, sex, race/ethnicity and other potential confounders. Individuals who were reclassified downward (0.7%) had higher risk than those who were not reclassified. Positive NRIs also support better overall reclassification by the CKD-EPI equation. Although we observed quantitative heterogeneity in some analyses, most of the studies were in agreement with the pooled results (eFigures 10-12). Importantly, a better risk categorization by the CKD-EPI equation as compared to the MDRD Study equation was consistent in almost all subgroups defined by age, sex, race/ethnicity, and clinical characteristics.

Our results confirm and extend results from previous literature. First, we observed that the CKD-EPI equation is a better predictor of risk than the MDRD Study equation in CKD
cohorts as well as in cohorts with higher eGFR. Improved or similar performance across the range of eGFR is important for clinical implementation. Second, although the elderly were less often reclassified by the CKD-EPI equation as compared to younger people, their future risk was also more correctly classified. Third, we found that the CKD-EPI equation predicts clinical risk more accurately than the MDRD Study equation in Asians. Although there is debate about which eGFR equation to use in Asia, our results suggest that the CKD-EPI equation would be a better option for risk prediction than the MDRD Study equation. Fourth, we showed that the CKD-EPI equation categorizes risk slightly more accurately than or at least as well as the MDRD Study equation in blacks, even though reclassification is less common in blacks than in whites and Asians. Fifth, we showed that the CKD-EPI equation provides more accurate risk categorization than the MDRD Study even after considering albuminuria, a measure of kidney damage. Recent reports suggest using albuminuria in addition to GFR for CKD staging and risk classification. Our findings suggest the CKD-EPI equation will be more useful than the MDRD Study equation for this application. Finally, we showed improved risk prediction for ESRD, in addition to mortality and cardiovascular disease shown in most of the previous studies.

The CKD-EPI and MDRD Study equations estimate the same physiologic function (GFR) using identical variables, thus the comparison of outcome prediction by two equations differs from the more common comparison of two models with and without a new biomarker. Since the same variables appear in both equations here, the difference in predicted risk between the two equations should not be expected to be as large as would be sought when adding a new biomarker. Consequently, we did not anticipate improvements in less sensitive statistics such as the c-statistic, which ignore absolute levels and categories and focus on ranking alone. This is particularly the case when age, sex, and race/ethnicity are included in the prediction model, since coefficients for these variables can compensate for worse prediction by eGFR

From another perspective, the use of the identical variables in the CKD-EPI requires no additional laboratory costs and enables relatively easy implementation with computerized algorithms. Therefore, a significant overall improvement in risk categorization by the CKD-EPI equation, even if small, would support its clinical use in place of the MDRD Study equation. At this time, only a small proportion of clinical laboratories in the US have switched to the CKD-EPI equation for eGFR reporting. In this context, clinically important reclassification crossing the threshold for CKD definition from CKD stage 3a to mildly reduced eGFR (60-89 ml/min/1.73m²) was observed in one third of individuals with eGFR MDRD 45-59 ml/min/1.73m² in our study. In the general population cohorts, these individuals had lower risk of mortality and ESRD as compared to those who were not reclassified (crude incidence rate difference −24.6 to −0.3 per 1,000 person-years and 20-51% lower adjusted hazard ratio). Given both lower CKD prevalence estimates and better risk categorization, the use of the CKD-EPI equation would contribute to a more efficient allocation of healthcare resources and more targeted prevention and management of CKD complications.

The paradoxically increased mortality risk at higher eGFR is noted in several studies and may be due to confounding by muscle wasting secondary to ill health. With the CKD-EPI equation, this risk was not evident in unadjusted analysis but was clearly evident after age adjustment suggesting the CKD-EPI equation does not fully overcome this limitation inherent to creatinine-based eGFR equations. Other filtration markers not related to muscle mass such as serum cystatin C might help to resolve this issue.

Some limitations of the present study should be mentioned. Measurements of creatinine were not standardized in all studies; however, we observed similar results when we limited
our analysis to studies with serum creatinine measurements standardized to IDMS (data not shown). Most of the participants recorded as blacks were from studies in the US. Although there are various ethnic groups within Asia, e.g., South Asian and Eastern Asian, we analyzed them together. Further analyses will be required for racial/ethnic groups not tested in this study.

Overall, the CKD-EPI creatinine-based equation more accurately classified individuals with respect to risk of mortality and ESRD as compared to the MDRD Study equation. Given more accurate GFR estimation, lower CKD prevalence estimates, and better risk categorization by the CKD-EPI equation without additional laboratory costs, its implementation for eGFR reporting could contribute to more efficient and targeted prevention and management of CKD-related outcomes.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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**Appendix**

**Author Contributions**

Dr. Coresh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Matsushita, Coresh for CKD-PC with CKD-PC investigators/collaborators listed below.


Drafting of the manuscript: Matsushita, Coresh, Levey.

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Statistical analysis: Matsushita, Woodward, Coresh with the Data Coordinating Center members listed below.

Obtained funding: Matsushita, Coresh for CKD-PC with cohort and collaborator support listed in eAppendix 3.

Administrative, technical, or material support: Matsushita, Mahmoodi, Coresh.

Study supervision: Matsushita, Coresh, Levey.
Conflict of Interest Disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. None of the authors reported conflicts.

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Kunitoshi Iseki, MD, University Hospital of the Ryukyus, Japan; **Pima Indian**

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Johan Arnlöv, MD, PhD, Uppsala University, Sweden; Lars Lannfelt, MD, PhD, Uppsala University Hospital, Sweden; Anders Larsson, MD, PhD, Uppsala University, Sweden; **ZODIAC**

Henk J. Bilo, MD, PhD, Isala Clinics, The Netherlands; Hanneke Joosten, MD, University Medical Center Groningen, The Netherlands; Nanno Kleefstra, MD, PhD, Isala Clinics, The Netherlands; Klaas H. Groenier, PhD, Isala Clinics, The Netherlands; Iefke Drion, MD, Isala Clinics, The Netherlands;

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Role of the Sponsor

The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

References


Figure 1.
Distribution based on kernel density estimation (proportion is for each integer eGFR) (A), and adjusted hazard ratios and 95% CIs (shaded areas or whisker plots) of all-cause mortality (B), cardiovascular mortality (C), and ESRD (D) according to eGFR by the CKD-EPI equation (red line) and the MDRD equation (black line) with eGFR 95 ml/min/1.73 m² as a reference (diamond). Vertical lines in panel A define GFR categories used for CKD staging.¹² Dots in panels B-D represent statistical significance (P<0.05). *Adjustments were for age, sex, race/ethnicity, smoking, history of CVD, systolic blood pressure, diabetes, serum total cholesterol concentration, body mass index, and albuminuria (log-ACR, log-PCR or categorical dipstick proteinuria [negative, trace, 1+, ≥2+]).
Figure 2.
Reclassification across eGFR categories by the CKD-EPI equation from eGFR categories based on the MDRD Study equation in the general population cohorts. The blue and red bars indicate upward reclassification to a higher eGFR category and downward reclassification to a lower eGFR category, respectively. Data are given as number (percentage) of participants who were reclassified.
Figure 3.
Meta-analyzed NRI (middle of data marker) and 95% CI (horizontal line) for the three outcomes based on eGFR categories overall and in subgroups according to demographic variables included in both equations and presence or absence of diabetes and hypertension (general population cohorts). The sizes of the data markers are proportional to the inverse of the variance of the NRIs. NRI was calculated as follows: \( \text{NRI} = \Pr(\text{down to lower eGFR category|events}) + \Pr(\text{up to higher eGFR category|no events}) - \Pr(\text{down to lower eGFR category|no events}) - \Pr(\text{up to higher eGFR category|events}) \). Positive NRI values favor the CKD-EPI equation.
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<th>%N</th>
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<th>% female</th>
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<th>% albuminuria</th>
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<th>mean age</th>
<th>% female</th>
<th>% blacks</th>
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<td>53%</td>
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Table 1
Characteristics of Participants according to Reclassification Status by CKD-EPI eGFR Equation Compared with MDRD Study Equation.
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<th>N</th>
<th>%N</th>
<th>mean</th>
<th>% female</th>
<th>% blacks</th>
<th>% albuminuria²</th>
<th>%N</th>
<th>mean</th>
<th>% female</th>
<th>% blacks</th>
<th>% albuminuria²</th>
<th>%N</th>
<th>mean</th>
<th>% female</th>
<th>% blacks</th>
<th>% albuminuria²</th>
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<td>93%</td>
<td>71</td>
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<td>95%</td>
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### Table 1

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<th>% blacks</th>
<th>% albuminuria (^2)</th>
<th>%N</th>
<th>mean age</th>
<th>% female</th>
<th>% blacks</th>
<th>% albuminuria (^2)</th>
<th>%N</th>
<th>mean age</th>
<th>% female</th>
<th>% blacks</th>
<th>% albuminuria (^2)</th>
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<td>Sunnybrook (^*)</td>
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<td>0%</td>
<td>83%</td>
<td>89%</td>
<td>71</td>
<td>44%</td>
<td>0%</td>
<td>84%</td>
<td>5%</td>
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<td>5%</td>
<td>66%</td>
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<tr>
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<td>8%</td>
<td>1%</td>
<td>77</td>
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<td>4%</td>
<td>15%</td>
</tr>
</tbody>
</table>

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

* Studies with urine albumin-to-creatinine ratio (ACR)

\(^{2}\) Studies with urine protein-to-creatinine ratio (PCR)

\(^{3}\) Proportion of participants with ACR ≥30 mg/g or PCR ≥50 mg/g or dipstick protein ≥1+. The study acronyms and abbreviations are listed in online supplement p 38-39.
Table 2
Incidence Rates and Adjusted Hazard Ratios (95% CIs) of Clinical Outcomes for those who were Reclassified by the CKD-EPI Equation Compared with those not Reclassified in General Population Cohorts

<table>
<thead>
<tr>
<th>MDRD eGFR category (ml/min/1.73 m²)</th>
<th>All-cause mortality (61,426 events)</th>
<th>Cardiovascular mortality (16,923 events)</th>
<th>ESRD (666 events)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Upward reclassification (5,586 events)</td>
<td>No reclassification (53,601 events)</td>
<td>Downward reclassification (2,239 events)</td>
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<tr>
<td>90+</td>
<td>Crude incidence rate (per 1,000 person-years)</td>
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<td>Adjusted hazard ratio</td>
<td>-</td>
<td>reference</td>
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<tr>
<td>60-89</td>
<td>Crude incidence rate (per 1,000 person-years)</td>
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<td>10.2</td>
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<td></td>
<td>Adjusted hazard ratio</td>
<td>1.03 (0.98-1.08)</td>
<td>reference</td>
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<td>45-59</td>
<td>Crude incidence rate (per 1,000 person-years)</td>
<td>9.9</td>
<td>34.5</td>
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<td></td>
<td>Adjusted hazard ratio</td>
<td>0.80 (0.74-0.86)</td>
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<tr>
<td>30-44</td>
<td>Crude incidence rate (per 1,000 person-years)</td>
<td>18.2</td>
<td>66.4</td>
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<tr>
<td></td>
<td>Adjusted hazard ratio</td>
<td>0.74 (0.61-0.88)</td>
<td>reference</td>
</tr>
<tr>
<td>15-29</td>
<td>Crude incidence rate (per 1,000 person-years)</td>
<td>33.4</td>
<td>88.1</td>
</tr>
<tr>
<td></td>
<td>Adjusted hazard ratio</td>
<td>1.04 (0.51-2.15)</td>
<td>reference</td>
</tr>
</tbody>
</table>

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

Adjusted for age, gender, race/ethnicity, smoking, systolic blood pressure, total cholesterol, diabetes, history of cardiovascular disease, body mass index, and albuminuria.