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Estimating GFR Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation: Better Risk Predictions

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Serum creatinine is measured more than 280 million times annually in the US, and more than 80% of clinical laboratories now report an estimated glomerular filtration rate (GFR) when serum creatinine is measured[1,2]. The most commonly used equation is the Modification of Diet and Renal Disease (MDRD) Study equation. Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) developed and validated a new equation, the CKD-EPI creatinine equation, which uses the same variables as the MDRD Study but is more accurate compared to measured GFR [2,3]. However, as for other diagnostic tests, other criteria are also important in clinical practice and public health, including detecting disease and predicting prognosis.

In this issue of *Circulation: Heart Failure*, McAlister and colleagues compare the CKD-EPI and MDRD Study equations for estimating prevalence of chronic kidney disease (CKD) and predicting mortality in a pooled individual patient dataset from 25 studies of 20754 heart failure patients included in the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) [4]. CKD was defined as estimated GFR <60 ml/min per 1.73 m^2 Mortality was defined as incidence per 1000 person years. During the average follow up interval of 2.0 years, 4981 patients died. The authors showed that the CKD-EPI equation reclassified more people to lower than higher eGFR categories and more accurately predicted mortality risk than the MDRD Study equation. The finding of more accurate risk prediction using the CKD-EPI equation is consistent with previously published studies comparing the two equations for prediction of adverse outcomes (Table)[5-9]. However, in most other studies, reclassification to higher eGFR categories was more common than reclassification to lower eGFR categories. Understanding these findings requires some discussion of the GFR estimating equations based on serum creatinine.

WHY USE GFR ESTIMATING EQUATIONS RATHER THAN SERUM CREATININE?

Clinical assessment of kidney function is part of routine medical care for adults. However, measuring GFR is cumbersome to perform, and therefore GFR is often estimated from the serum concentration of endogenous filtration markers. GFR estimating equations

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incorporate demographic and clinical variables as surrogates for the non-GFR determinants of these filtration markers[10]. Age, sex, race and body weight are surrogates for creatinine generation from muscle, which affects serum creatinine concentration independently from GFR. GFR estimating equations provide a more accurate estimate of measured GFR than the serum level of the filtration marker alone. In addition, GFR estimates are provided in the same units as measured GFR, thereby simplifying clinical decisions based on the level of kidney function.

An important consideration when evaluating the performance of estimating equations is the assay used in their development. The most common cause of inaccuracy in creatinine assays is interference by non-creatinine moieties in the serum that react with the creatinine assay, leading to overestimation of the serum creatinine concentration, especially at low values. More accurate creatinine assays, traceable to gold-standard creatinine measurements, are now available, and a creatinine standardization program has been implemented in all clinical laboratories throughout the US [11]. The effect of standardizing creatinine assays will vary among clinical laboratories but on average will lead to lower values for serum creatinine and higher values for estimated GFR compared to before standardization. The MDRD Study equation has now been re-expressed for use with standardized values and CKD-EPI equation was developed using standardized creatinine [3,12]. Variation among creatinine assays is relevant when categorizing people by level of GFR, since a systematic difference in assays, even if causes only a small difference in estimated GFR, can lead to reclassification to a different category[13]. Thus, when determining prevalence of CKD or categories of estimated GFR, attention to the creatinine assay used is particularly important. When comparing GFR estimating equations, it is essential to use the form of the equation that is expressed for the serum creatinine assay used in the study population.

HOW DOES THE CKD-EPI EQUATION COMPARE TO THE MDRD STUDY EQUATION?

Accuracy compared to measured GFR

The MDRD Study equation was developed in 1999 using data from a study of 1628 people using non-standardized serum creatinine assays and re-expressed for use with standardized creatinine in 2006.[12,14] Because it was developed in a population with CKD, it underestimates measured GFR at higher levels. The CKD-EPI equation was developed in 2009 using data from 8254 people with and without CKD in 10 studies and validated in 3896 people in 16 separate populations[3]. Creatinine assays for all studies were standardized to higher order reference materials[15] When used with standardized creatinine assays, the CKD-EPI equation generally yields higher levels for eGFR than the MDRD Study equation, especially for younger people, whites and women. In the original report, the CKD-EPI equation was more accurate than the MDRD Study equation, especially at higher ranges of GFR [2,3]. Based on this finding, the CKD-EPI investigators concluded that the CKD-EPI equation should replace the MDRD Study equation in clinical practice and that GFR estimates should be reported throughout the range. Since then, there have been several publications which comparing the CKD-EPI and MDRD Study equations, which have generally confirmed the greater accuracy of the CKD-EPI equation in estimating measured GFR[16].

Detecting and staging disease

In principle, decreased GFR in acute and chronic kidney diseases is preceded by alterations in structure that can be detected by pathologic disturbances or makers of kidney damage. Biopsies are usually not obtained in clinical practice and markers of kidney damage are not sensitive for all kidney diseases, thus in many patients, decreased GFR is the earliest sign of

kidney disease. Widespread reporting of eGFR simplifies the detection GFR <60 ml/min/ 1.73 m^2, one of the criteria for CKD.

Higher eGFR using the CKD-EPI equation would reduce the false positive diagnoses of CKD based on eGFR compared to the MDRD Study equation. The CKD-EPI investigators compared the eGFR distribution and CKD prevalence using the CKD-EPI and MDRD Study equations among 16,032 adult participants in the US National Health and Nutrition Examination Surveys (NHANES 1999-2006), a nationally representative survey of non-institutionalized persons in the US[3] . Median eGFR was higher with the CKD-EPI equation compared to the MDRD Study equation (94.5 vs. 85.0 ml/min/1.73 m^2, respectively), and CKD prevalence was lower (11.6% vs. 13.1%, respectively).

In the study by McAlister et al, prevalence of CKD (estimated GFR < 60 ml/min per 1.73 m2) was 51% using the MDRD Study equation and 55% using the CKD-EPI equation. Overall, the CKD-EPI equation reclassified 3760 (18%) patients to different GFR categories than the MDRD Study equation. Of those reclassified, 18% were placed in a higher GFR category and the remaining 82% were placed in a lower GFR category. We suspect that the higher prevalence of CKD using the CKD-EPI equation and more frequent reclassification to lower rather than higher GFR categories in this study likely reflects an error arising from using the CKD-EPI equation with non-standardized creatinine assays. The CKD-EPI equation is expressed for standardized values, which were 5% lower than non-standardized values in the research laboratory used for the development of the MDRD Study and CKD-EPI equations. The form of the MDRD Study equation used in the analyses by McAlister et al is appropriate for use with non-standardized creatinine values, which is appropriate, since it is most likely that among the 25 studies included in MAGGIC, the majority of the creatinine measurements were performed prior to the standardization program. However, using these higher creatinine values in the CKD-EPI equation would lead to lower estimated GFR than was intended by the equation. Other studies have accounted for this difference in creatinine assays by reducing the non-standardized serum creatinine assays by 5% for use with the MDRD Study and CKD-EPI equations that are expressed for standardized creatinine, thus enabling a “fair comparison” of eGFR computed using both equations[6].

Predicting Prognosis

Decreased GFR is now a well-established risk factor for cardiovascular disease (CVD) and mortality, as well as kidney failure [17,18] . There is now an increasing literature on the advantage of the CKD-EPI equation compared to the MDRD Study equation for prediction of risk in general population samples[8] and patients at high risk for CKD [5,7], and in patients with cardiovascular disease[6,9] (Table). In these studies, the individuals reclassified to higher eGFR using the CKD-EPI equation generally had lower risk than those not re-classified, while those reclassified to lower eGFR generally had a higher risk than those not re-classified.

The current paper contributes to the literature by comparing these equations in patients with heart failure, and overall, the results seem to confirm the findings from the previous studies. The CKD-EPI estimated GFR provided a better risk prediction than the MDRD Study equation [AUC of 0.644 (0.635-0.653) vs 0.634 (0.626-0.644)]. For example, in those reclassified from MDRD Study equation eGFR category 45-59 ml/min per 1.73 m^2 (CKD stage 3) to a higher eGFR category (60-74 ml/min/1.73 m^2, no CKD) using the CKD-EPI equation, the mortality rate was 101 (95% confidence intervals 74-135) per 1000 person years, which was lower than those not reclassified [142 (133-151)] and those reclassified to a lower eGFR category [204.9 (18-229)]. Thus, despite the error in creatinine calibration, the study by McAlister et al is consistent with other studies in that patients with lesser risk

appear to be reclassified to higher GFR and patients with higher risk appear to be reclassified to lower GFR.

WHERE DO WE GO FROM HERE?

The CKD-EPI creatinine equation is currently the most accurate method for estimating GFR for diverse populations. Compared to the MDRD Study equation, the CKD-EPI equation permits more accurate GFR estimation, fewer false positive diagnosis of CKD, lower prevalence estimates for CKD, and more accurate risk prediction for adverse outcomes. This accumulating evidence supports the recommendations of the CKD-EPI investigators that the CKD-EPI equation should replace the MDRD Study equation for general use [3] . There are few drawbacks to more widespread implementation of the CKD-EPI equation[z]. Implementing a new GFR estimating equation requires an ongoing educational effort to understanding its strengths and limitations, similar to advances in other diagnostic tests. Since the same four variables are used, the impact on information systems is minimal, and the differences observed by clinicians will be equivalent to reporting any analyte using a new assay.

We have come a long way since serum creatinine alone was used for GFR estimation. Despite these improvements in GFR estimation, much uncertainty remains. More research is required to determine the usual levels of GFR and non-GFR determinants of creatinine in representative populations, including the elderly and diverse racial and ethnic groups, and to determine the optimal application of GFR estimates in clinical medicine and public health. The availability of additional filtration markers in that are less dependent on muscle mass, such as cystatin C, offers the promise of even more accurate GFR estimates[20].

References

1. Miller WG. Estimating glomerular filtration rate. Clin Chem Lab Med. 2009; 47:1017–1019. [PubMed: 19728841]
2. Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, Hamm LL, Lewis JB, Mauer M, Navis GJ, Steffes MW, Eggers PW, Coresh J, Levey AS. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis. 2010; 56:486–495. [PubMed: 20557989]
3. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimateglomerular filtration rate. Ann Intern Med. 2009; 150:604–612. [PubMed: 19414839]
4. McAlister FA, Ezekowitz JA, Tarantini L, Squire I, Komajda M, Bayes-Genis A, Gotsman I, Whalley G, Earle N, Poppe KK, Doughty RN. Renal Dysfunction in Heart Failure Patients with Preserved versus Reduced Ejection Fraction: Impact of the New CKD-EPI Formula. Circulation: Heart Failure. 2012; 5:XXX–XXX.
5. Stevens LA, Li S, Kurella Tamura M, Chen SC, Vassalotti JA, Norris KC, Whaley-Connell AT, Bakris GL, McCullough PA. Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study Equations: Risk Factors for and Complications of CKD and Mortality in the Kidney Early Evaluation Program (KEEP). American journal of kidney diseases : the official journal of the National Kidney Foundation. 2011; 57:S9–S16. [PubMed: 21338849]
6. Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD. Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. Am Heart J. 2011; 162:548–554. [PubMed: 21884875]

7. White SL, Polkinghorne KR, Atkins RC, Chadban SJ. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. Am J Kidney Dis. 2010; 55:660–670. [PubMed: 20138414]
8. Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis. 2010; 55:648–659. [PubMed: 20189275]
9. AlFaleh HF, Alsuwaida AO, Ullah A, Hersi A, AlHabib KF, AlShahrani A, AlNemer K, AlSaif S, Taraben A, Ahmed WH, Balghith MA, Kashour T. Glomerular filtration rate estimated by the CKD-EPI formula is a powerful predictor of in-hospital adverse clinical outcomes after an acute coronary syndrome. Angiology. 2012; 63:119–126. [PubMed: 21602255]
10. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med. 2006; 354:2473–2483. [PubMed: 16760447]
11. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, Hostetter T, Levey AS, Panteghini M, Welch M, Eckfeldt JH. National Kidney Disease Education Program Laboratory Working Group. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clinical Chemistry. 2006; 52:5–18. [PubMed: 16332993]
12. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006; 145:247–254. [PubMed: 16908915]
13. Coresh J, Eknoyan G, Levey AS. Estimating the prevalence of low glomerular filtration rate requires attention to the creatinine assay calibration. J Am Soc Nephrol. 2002; 13:2811–2812. author reply 2812-2816. [PubMed: 12397055]
14. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F. Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007; 53:766–772. [PubMed: 17332152]
15. Stevens LA, Manzi J, Levey AS, Chen J, Deysher AE, Greene T, Poggio ED, Schmid CH, Steffes MW, Zhang YL, Van Lente F, Coresh J. Impact of creatinine calibration on performance of GFR estimating equations in a pooled individual patient database. Am J Kidney Dis. 2007; 50:21–35. [PubMed: 17591522]
16. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating Equations for Glomerular Filtration Rate in the Era of Creatinine Standardization: A Systematic Review. Ann Intern Med. 2012
17. Chronic Kidney Disease Prognosis Consortium. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010; 375:2073–2081. [PubMed: 20483451]
18. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011; 80:17–28. [PubMed: 21150873]
19. Becker BN, Vassalotti JA. A software upgrade: CKD testing in 2010. Am J Kidney Dis. 2010; 55:8–10. [PubMed: 20053344]
20. Inker LA, Eckfeldt J, Levey AS, Leiendecker-Foster C, Rynders G, Manzi J, Waheed S, Coresh J. Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) Cystatin C Equations for Estimating GFR With Standardized Serum Cystatin C Values. Am J Kidney Dis. 2011; 58:682–684. [PubMed: 21855190]

Table

Studies comparing MDRD Study and CKD-EPI equations for long term risk

Author, Date, Study	Population Description, number of participants	Age*	eGFR > 60 ml/min/1.73 m^2 (%)	Creatinine assay calibration^	Outcomes	Relative risk in those classified by the CKD-EPI equation to a higher GFR category ⁊	Relative risk in those classified by the CKD-EPI equation to a lower GFR category ⁊
McAllister 2012; MAGGIC	Heart failure, *n*=20,754	68	55	N	All-cause mortality	↓	↑
AlFaleh; 2012; SPACE	Acute coronary syndrome, *n* =5,034	58	74	N	In-hospital mortality	NR	NR
Skali et al; 2011; VALIANT	AMI with heart failure, *n* =14,527	66	69	Y	Composite of cardiovascular death, congestive HF, recurrent MI, or stroke	↓	↑
Stevens; 2010 KEEP	High risk, *n* =116,321	55**	86	Y	All-cause mortality	↓	↑
White; 2010; AusDiab	High risk, *n* = 11,247	52	93	Y	All-cause mortality	↓	NR
Matsushita; 2010; ARIC	General population, *n* =13,905	54	98	Y	ESRD, all-cause mortality, coronary heart disease, stroke	↓ for all outcomes	↑ for all outcomes

Studies identified by searching Medline for studies that have compared the CKD-EPI and MDRD Study equations for prognosis

*Mean or median, as reported in the paper or weighted mean calculated across subgroups

^Assay calibration appropriate for each equation

⁊Compared to those not reclassified

**Mean age from KEEP population reported separately

MAGGIC,Meta-analysis Global Group in Chronic Heart Failure; SPACE; The Saudi Project for Assessment of Coronary Events; VALIANT; Valsartan in Acute Myocardial Infarction Trial; AMI, Acute Myocardial Infarction; KEEP, Kidney Early Evaluation Program; AusDiab; Australian Diabetes, Obesity and Life Style Study Survey; ARIC Atherosclerosis Risk in Communities; ESRD, End Stage Renal Disease; N, no; Y, yes; NR, Not Reported;