Clinical Chemistry 55:9
000–000 (2009)

Perspective: Assessment of Kidney Function for Drug Dosing

Andrew S. Narva*

The effort to improve the identification and management of patients with chronic kidney disease (CKD)[1] is based on implementing more precise means of assessing kidney function and kidney damage in the clinical setting. Over the past decade, the clinical chemistry community has adopted routine reporting of estimated GFR (eGFR) calculated from the Modification of Diet in Renal Disease (MDRD) Study and is implementing a creatinine standardization program to enable the manufacturers of laboratory methods to establish calibration traceability to an isotope-dilution mass spectrometry (IDMS) reference measurement procedure. As a result, routine reporting of eGFR based on an IDMS-traceable creatinine is becoming the clinical standard for patient care *(1, 2)*.

As with all changes in clinical practice, the implementation of eGFR reporting and creatinine standardization has created some uncertainty and confusion among health care providers. A focus of concern is the assessment of kidney function for drug dosing adjustment. Standardizing creatinine calibration to an IDMS reference produces a lowering of creatinine values by 10%–20% for most methods. Pharmaceutical manufacturers have used the Cockcroft–Gault (CG) equation to estimate creatinine clearance as the basis for drug dose adjustment recommendations, and there is no modified equation available for use with the IDMS-traceable creatinine results. Consequently, creatinine clearance estimated from the CG equation will be erroneously high. Because eGFR using the MDRD equation is relatively new, eGFR data is not part of drug safety information or package inserts approved by the US Food and Drug Administration (FDA). Clinicians are most concerned about dosing highly toxic drugs with narrow therapeutic indices, particularly carboplatin, an antineoplastic agent.

Some clinical chemists have experienced resistance to creatinine standardization from clinicians in their facilities based on their uncertainty about how standardization would affect their ability to dose drugs such as carboplatin. Other clinicians have responded by requesting back-calculation to a nonstandardized creatinine which can then be used in the CG equation. Both of these responses reflect some misunderstanding about creatinine measurement. The first misunderstanding concerns the nature of estimating equations. The goal is to develop an equation that produces an eGFR which is closest to a gold standard, in this case a measured GFR. Estimating equations are developed from populations of patients and will give results that reflect the mean GFR of the population in which they were developed. However, the actual GFR of any individual will be distributed about that mean value. Thus, an estimating equation provides the "best guess" of the GFR of a patient based on patient-specific values supplied for the variables used in that equation (in the case of the MDRD equation, age, sex, race, and creatinine); however, it needs to be emphasized that such an estimated GFR is not the patient's actual GFR. It has been demonstrated that the MDRD equation is superior to the CG equation in predicting kidney function in most people *(3)*.

The second misunderstanding concerns the impact of nonstandardized creatinines on the CG equation. Although the CG estimation has been the traditional means of assessing kidney function and is the method with which pharmacists and clinicians have become comfortable, it has been subject to the variation in creatinine values that occurred before standardization. Rather than providing a clinical gold standard, Cockcroft–Gault estimates likely varied depending on the creatinine method used in any given facility. Because this variation is a function of method and facility, it is not possible to use a single correction factor to back-calculate to the nonstandardized value.

A recent article by Stevens and collaborators *(4)* shows that efforts at back-calculation are not necessary. As part of a collaborative effort that pools data from 5504 individuals from a range of research stud-

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD.
* Address correspondence to the author at: National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Two Democracy Plaza, Room 645, 6707 Democracy Blvd., Bethesda, MD 20892-0001. Fax 301-480-3510; e-mail narvaa@niddk.nih.gov.
Received May 7, 2009; accepted June 25, 2009.
Previously published online at DOI: 10.1373/clinchem.2009.127944
[1] Nonstandard abbreviations: CKD, chronic kidney disease; eGFR, estimated GFR; MDRD, Modification of Diet in Renal Disease; IDMS, isotope-dilution mass spectrometry; CG, Cockcroft–Gault; FDA, US Food and Drug Administration; NKDEP, National Kidney Disease Education Program.

ies and clinical populations, Stevens and her colleagues compared measured GFR (iothalamate clearance) with 3 estimating equations used in drug dose adjustments, the MDRD Study equation, the CG equation incorporating the actual weight, and the CG equation using ideal body weight (CG_{IBW}). The 3 estimating methods were compared with measured GFR in placing individuals in the kidney function categories established by the FDA for drug dosing adjustment. The investigators then compared the differences in recommended dosing for the 5504 study patients that would result from using the 3 equations for 15 different medications cleared by the kidneys. IDMS-standardized creatinine values were used in all equations. The IDMS-traceable version of the MDRD Study equation was used, but as noted above, there is no IDMS-traceable version of the CG equation. Kidney function was expressed for all 3 calculations in mL/min (not adjusted for body surface area), the units used for drug dosing labels.

Results of the comparison showed that the MDRD equation demonstrated greater concordance (78%) with assignment to FDA kidney function drug dosing categories by measured GFR than CG_{IBW} (66%) or CG (73%). Concordance for drug dosing recommendations based on measured GFR for the 15 renally cleared drugs was also best for MDRD (88%) compared to CG_{IBW} (82%) and CG (85%). Of the 3 estimating methods, the CG equation was most likely to generate higher recommended drug dosages, and CG_{IBW} was most likely to generate lower recommended drug dosages.

Of key interest to practitioners was the comparison between the dosing recommendations by the 3 methods. Overall concordance of recommended drug dosing was 89% between the MDRD and CG equations and 88% between MDRD and CG_{IBW}. The MDRD produced recommendations that were lower than CG in 9% of the study population and higher in 10% when the CG_{IBW} was used.

Stevens and her colleagues have shed some light on a controversy over which substantial concern has been generated. Although all currently used equations for estimating kidney function are subject to the problems associated with using creatinine as a marker, and while no prediction equation is perfect for all patients, reliance on the CG as the sole method of estimating kidney function for drug dosing purposes does not appear to be supported by the data from this large study. They have demonstrated that the MDRD equation is most concordant with FDA guidelines for kidney function stratification for drug dosing adjustment.

There are several reasons we should encourage use of the MDRD equation for drug dosing adjustment. It is the only method that was developed to be used with standardized creatinine and will produce consistent dosing recommendations. It is also the standard for identifying and monitoring patients with kidney disease in the clinical and public health settings. The advantage of using 1 method for all or most clinical purposes is obvious, especially for assessing kidney function, a task that many providers find confusing, if not intimidating.

The National Kidney Disease Education Program (NKDEP) will soon publish an educational advisory for clinicians on estimating kidney function for drug dosing purposes. The advisory will encourage the use of MDRD or CG estimating equations and, when there is concern that estimated kidney function is not adequate for patient safety or there is a distinct difference in recommended dose between the 2 methods, will suggest consideration of measured creatinine clearance or direct measurement of GFR. The advisory will describe the bias inherent in using standardized creatinine in the CG equation and the pitfalls of back-calculation to a nonstandardized creatinine using a single correction factor.

How can clinical chemists help? Health care providers rely on clinical chemists to clarify the science and physiology of laboratory measurements. Clinical chemists can help educate providers on the utility as well as the limits of eGFR and other methods. The NKDEP Laboratory Working Group has developed materials to facilitate better understanding of laboratory tools for the assessment of kidney function and damage. We encourage clinical chemists to use these educational tools and to recommend revisions or development of additional tools. Educating providers about these laboratory tests is essential, not only for patient care, but to maintain credibility for the future when clinicians will need encouragement to use the newer and better markers of kidney function that will inevitably replace creatinine-based estimates of GFR.

Author Contributions: *The author confirmed he has contributed to the intellectual content of this paper and has met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures of Potential Conflicts of Interest: *The author declared no potential conflicts of interest.*

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References

1. Accetta NA, Gladstone EH, Disogra C, Wright EC, Briggs M, Narva AS. Prevalence of estimated GFR reporting among US clinical laboratories. Am J Kidney Dis 2008;52:778–87.
2. Miller, WG. Reporting estimated GFR: a laboratory perspective. Am J Kidney Dis 2008;52:645–8.
3. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 2005;16:459–66.
4. Stevens LA, Nolin TD, Richardson MM, Feldman HI, Lewis JB, Rodby R, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis 2009;54:33–42.
5. National Kidney Disease Education Program. http://nkdep.nih.gov (Accessed May 24, 2009).