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August 2019

Vol. 21, No. 3

Our Mission: Helping to prepare Iowa's health practitioners to care for our growing population of elders. *E-NEWS* is one of our methods of teaching through technology.

Each month, *E-NEWS* delivers abstracts from current multidisciplinary healthcare journal articles related to a specific geriatric topic. This month's *E-NEWS* focuses on KIDNEY FUNCTION AND MEDICATION DOSING ADJUSTMENTS IN THE OLDER ADULT.

KIDNEY FUNCTION AND MEDICATION DOSING ADJUSTMENTS IN THE OLDER ADULT

In this issue of the *E-NEWS*, you will find abstracts for:

- A study that compares the estimation of renal function obtained with various equations and evaluates the implication of their use for drug dosing in older adults.
 - A study that evaluates the performance of creatinine-based equations for estimating glomerular filtration rate in older adults.
 - A study that seeks to determine discrepancies between two renal function equations and the implications for refining drug dosage adjustment strategies.
 - An article that discusses drug therapy management in patients with renal impairment.
 - A study that investigates the discrepancy between equations estimating kidney function in geriatric care and the implication for drug prescription.
 - A study that examines the importance of correct estimation of renal function for drug treatment in hospitalized older adults, especially women.
 - An article that presents the pragmatic use of kidney function estimates for drug dosing.
 - An article that addresses the role of deprescribing in older adults with chronic kidney disease.
 - A study that explores the application of prescribing recommendations in older adults with reduced kidney function.
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- Cartet-Farnier E, Goutelle-Audibert L, Maire P, De la Gastine B, Goutelle S. Implications of using the MDRD or CKD-EPI equation instead of the Cockcroft-Gault equation for estimating renal function and drug dosage adjustment in elderly patients. *Fundam Clin Pharmacol*. 2017 Feb;31(1):110-119.

The objectives of this study were to compare the estimations of renal function obtained with six equations, including the Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations and to evaluate the implication of using other equations for drug dosing in elderly patients in place of CG. An observational prospective study was conducted over 6 months in two geriatric hospitals with inclusions of all hospitalized inpatients. A list of 36 drugs for which recommendations of dosage adjustment for renal function were mentioned in the manufacturer dosing guidelines was used to compare the implications of using the various equations for drug dosing. A total of 249 patients with a mean age of 83.6 years were included. Mean estimates of renal function from the CG, MDRD, and CKD-EPI equations were 51.3 ± 23.5 mL/min, 72.2 ± 35.2 , and 64.3 ± 22.5 mL/min/1.73 m², respectively ($P < 0.001$). Twenty percent of patients had at least one drug for which the dose was not appropriately adjusted to renal function. The use of the MDRD and CKD-EPI equations in place of the CG equation was associated with dosage discrepancy in 20-25% of patients and 15% of drug orders, resulting in potential overdosage in 95% of cases. Use of MDRD or CKD-EPI equations results in higher estimates of renal function and may have important implications for drug dosing decision and drug safety in elderly patients. The best way is to directly measure the drug effect or its concentration when it is possible to do so. © Société Française de Pharmacologie et de Thérapeutique.



- da Silva Selistre L, Rech DL, de Souza V, Iwaz J, Lemoine S, Dubourg L. Diagnostic Performance of Creatinine-Based Equations for Estimating Glomerular Filtration Rate in Adults 65 Years and Older. *JAMA Intern Med*. 2019 Apr 29. doi: 10.1001/jamainternmed.2019.0223. [Epub ahead of print]

Importance: Estimating glomerular filtration rate (GFR) is useful in many clinical conditions. However, very few studies have evaluated the performance of GFR-estimating equations in older adults at various degrees of kidney impairment. Objective: To determine the performance of plasma-creatinine-based equations Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI), Lund-Malmö Revised, (LMR), full age spectrum (FAS), and Berlin Initiative Study (BIS) 1 in older adults across a broad spectrum of GFRs. Design, Setting, and Participants: Single-center cross-sectional study performed in France including 2247 participants aged 65 to 90 years who underwent inulin GFR measurements from July 1, 2003, to July 30, 2017, for suspected or established renal dysfunction, for renal risk, before kidney donation, or after kidney transplant. Main Outcomes and Measures: The main outcome measure was GRF measured by inulin clearance. Equation performance criteria considered bias (difference between estimated and measured GFR), precision (interquartile range of the median difference), and accuracy P30 (percentage of estimated GFRs lying between [measured GFR - 30% of measured GFR] and [measured GFR + 30% of measured GFR]). Results: The mean (SD) age of the 2247 participants was 71.5 (5) years and 1192 (53.0%) were male. The difference in median (95% CI) bias was significant between CKD-EPI vs LMR (-4.0 [-4.0 to -3.5 mL/min/1.73 m²; $P < .001$]) and CKD-EPI vs FAS (-2.0 [-3.5 to -2.5] mL/min/1.73 m², $P < .001$) but not significant between CKD-EPI vs BIS 1 (0.0 [-1.5 to 0.5], $P = .07$, Mood test). In patients aged 65 to 74 years with measured GFR < 45 mL/min/1.73 m², the difference in median P30 (95% CI) was not significant between CKD-EPI vs LMR ($P = .08$) and CKD-EPI vs FAS ($P = .48$) but significant vs BIS 1 ($P = .004$, McNemar test). In subjects 75 years and older, with measured GFR less than 45 mL/min/1.73 m², LMR and BIS 1 were more accurate than CKD-EPI and FAS (P30 = 74.5 [70.0-79.5] and 73.0 [68.0-78.0] vs 69.0 [64.5-74.0] and 69.0 [65.5-72.0]). In all patients, despite small statistical differences, the performance of CKD-EPI equation was not clinically different from that of LMR, FAS, or BIS 1. Conclusions and Relevance: In a referral group of patients 65 years and older who had GFR estimated using CDK-EPI, LMR, BIS 1, and FAS equations, a comparison with renal inulin clearance found that none of the equations had a superior diagnostic performance. Each had limitations regarding accuracy.



- Delanaye P, Guerber F, Scheen A, Ellam T, Bouquegneau A, Guergour D, Mariat C, Pottel H. Discrepancies between the Cockcroft-Gault and Chronic Kidney Disease Epidemiology (CKD-EPI) Equations: Implications for Refining Drug Dosage Adjustment Strategies. *Clin Pharmacokinet.* 2017 Feb;56(2):193-205.

INTRODUCTION: The dosages of many medications require adjustment for renal function. There is debate regarding which equation, the Chronic Kidney Disease Epidemiology (CKD-EPI) equation vs. the Cockcroft-Gault (CG) equation, should be recommended to estimate glomerular filtration rate. METHODS: We used a mathematical simulation to determine how patient characteristics influence discrepancies between equations and analyzed clinical data to demonstrate the frequency of such discrepancies in clinical practice. In the simulation, the modifiable variables were sex, age, serum creatinine, and weight. We considered estimated glomerular filtration rate results in mL/min, deindexed for body surface area, because absolute excretory function (rather than per 1.73 m² body surface area) determines the rate of filtration of a drug at a given plasma concentration. An absolute and relative difference of maximum (\pm) 10 mL/min and 10 %, respectively, were considered concordant. Clinical data for patients aged over 60 years (n = 9091) were available from one hospital and 25 private laboratories. RESULTS: In the simulation, differences between the two equations were found to be influenced by each variable but age and weight had the biggest effect. Clinical sample data demonstrated concordance between CKD-EPI and CG results in 4080 patients (45 %). The majority of discordant results reflected a CG result lower than the CKD-EPI equation. With aging, the CG result became progressively lower than the CKD-EPI result. When weight increased, the opposite occurred. DISCUSSION: The choice of equation for excretory function adjustment of drug dosage will have different implications for patients of different ages and body habitus. CONCLUSIONS: The optimum equation for drug dosage adjustment should be defined with consideration of individual patient characteristics.

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- Eppenga WL, Kramers C, Derijks HJ, Wensing M, Wetzels JF, De Smet PA. Drug therapy management in patients with renal impairment: how to use creatinine-based formulas in clinical practice. *Eur J Clin Pharmacol.* 2016 Dec;72(12):1433-1439.

PURPOSE: The use of estimated glomerular filtration rate (eGFR) in daily clinical practice. METHODS: eGFR is a key component in drug therapy management (DTM) in patients with renal impairment. eGFR is routinely reported by laboratories whenever a serum creatinine testing is ordered. In this paper, we will discuss how to use eGFR knowing the limitations of serum creatinine-based formulas. RESULTS: Before starting a renally excreted drug, an equally effective drug which can be used more safely in patients with renal impairment should be considered. If a renally excreted drug is needed, the reliability of the eGFR should be assessed and when needed, a 24-h urine creatinine clearance collection should be performed. After achieving the best approximation of the true GFR, we suggest a gradual drug dose adaptation according to the renal function. A different approach for drugs with a narrow therapeutic window (NTW) is recommended compared to drugs with a broad therapeutic window. For practical purposes, a therapeutic window of 5 or less was defined as a NTW and a list of NTW drugs is presented. Considerations about the drug dose may be different at the start of the therapy or during the therapy and depending on the indication. Monitoring effectiveness and adverse drug reactions are important, especially for NTW drugs. Dose adjustment should be based on an ongoing assessment of clinical status and risk versus the benefit of the used regimen. CONCLUSION: When determining the most appropriate dosing regimen serum creatinine-based formulas should never be used naively but always in combination with clinical and pharmacological assessment of the individual patient.

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- Guerville F, Roubaud-Baudron C, Duc S, Salles N, Rainfray M, Bourdel-Marchasson I. Discrepancy Between Equations Estimating Kidney Function in Geriatric Care: A Study of Implications for Drug Prescription. *Drugs Aging.* 2019 Feb;36(2):155-163.

BACKGROUND: In older patients, the agreement is low between creatinine clearance estimated with the Cockcroft-Gault equation (eCrCl) and glomerular filtration rate estimated with the Chronic Kidney Disease Epidemiology Collaboration equation (eGFRCKD-EPI). The implications of these discrepancies for drug prescription have so far been assessed only for a few selected molecules. OBJECTIVE: The aim of this study was to investigate the proportion of geriatric patients receiving drugs with a different recommended dose or indication (i.e. an adjustment discrepancy) depending on eCrCl versus eGFRCKD-EPI estimates of kidney function. METHODS: Patients admitted to acute geriatric care units in our university hospital were eligible for

inclusion. All drug classes were studied. We retrospectively determined recommended prescriptions according to eCrCl and eGFRCKD-EPI. RESULTS: Sixty percent of patients received at least one drug requiring dose adjustment and/or received a drug with a relative contraindication based on their estimated kidney function. Thirty-one percent of patients received at least one drug with an adjustment discrepancy: 20% received at least one drug for which the recommended dose differed depending on eCrCl versus eGFRCKD-EPI estimates of kidney function, 4% received a drug with a relative contraindication according to eCrCl but not eGFRCKD-EPI, and 7% received both. Factors independently associated with an adjustment discrepancy were older age and lower weight. Main drug classes involved were benzodiazepines, anticoagulants, and anti-microbial drugs. CONCLUSION: In acute geriatric care units, recommended drug dose adjustments are frequently discordant according to the equations used to estimate kidney function, notably for benzodiazepines, anticoagulants, and anti-microbial drugs. The consequences for treatment efficacy and safety should be investigated.

- Helldén A, Bergman U, Odar-Cederlöf I. The importance of correct estimation of renal function for drug treatment in hospitalized elderly patients, especially women: A prospective observational study. *Clin Nephrol.* 2019 Apr;91(4):254-264.

AIM: To compare renal function by several GFR formulas (particularly cystatin C eGFR-"CAPA") in relation to renal risk drugs (RRDs) in patients admitted to two geriatric wards in a university geriatric department. MATERIALS AND METHODS: This was a prospective quality improvement study including 108 patients, 2/3 women, age ≥ 75 years, admitted with multimorbidity. Renal function tests were performed with Cockcroft & Gault with uncalibrated (C&Guc) and calibrated creatinine (C&Gcc), and 3 - 4 points' iohexol clearance (mGFR) in mL/min, and eGFR with MDRD4, CKD-EPI, CAPA, and BIS2 clearance in mL/min/1.73m². Agreement was tested by Bland & Altman analysis. The number and type of RRDs were analyzed. RESULTS: Measured GFR, C&Gcc, and C&Guc were mean 37, 39, and 32 mL/min, respectively. Estimated GFR by MDRD4, CKD-EPI, CAPA, and BIS2 were mean 56, 52, 45, and 40 mL/min/1.73m², respectively. Compared to mGFR, women had significantly higher clearance for all estimates except for C&Gcc and C&Guc. C&Gcc, C&Guc, and BIS2 showed the lowest bias. 38 RRDs were identified. 96 patients used a mean of 2.3 RRDs per patient, and 1.7 RRDs needed dose adjustments. Cardiovascular drugs and analgesics were the most frequent RRDs. DISCUSSION: The C&Gcc, C&Guc, and BIS2 equations gave the best estimate of kidney function in relation to mGFR for drug dosing in the elderly. The eGFR methods showed significantly higher clearance than mGFR, C&Gcc, C&Guc, and BIS2. RRDs that needed dose adjustment were common in this geriatric population. If the eGFR formulas (MDRD4, CKD-EPI, and CAPA) are used instead of C&Gcc, C&Guc, and BIS2, higher and potentially more risky doses of RRDs may be administered to geriatric patients over 75 years, women in particular.

- Hudson JQ, Nolin TD. Pragmatic Use of Kidney Function Estimates for Drug Dosing: The Tide Is Turning. *Adv Chronic Kidney Dis.* 2018 Jan;25(1):14-20.

Creatinine clearance has been the most common method of estimating kidney function for the purpose of drug dosing for decades. The availability and extensive clinical use of estimated glomerular filtration rate (eGFR) now provides clinicians a potential alternative. Currently, data demonstrating the validity of eGFR-based drug dosing is limited, but proof of principle has been established and the tide related to use of eGFR for drug dosing appears to be turning. Use of the same kidney function estimate for management of kidney disease, drug development and dosing, and harmonization in all clinical arenas would be ideal. Use of multiple equations can lead to differences in kidney function estimates and corresponding drug dosing regimens, which necessitates clinical judgment and a pragmatic approach when rendering drug dosing decisions. Careful consideration of the risk-benefit ratio of individual drugs and dosing regimens within each patient is warranted. Going forward, FDA guidance will likely incentivize pharmaceutical manufacturers to generate eGFR-based dosing recommendations in addition to creatinine clearance for inclusion in the label of newly approved drugs. However, dosing information for currently approved drugs will continue to be based on creatinine clearance alone, so clinicians must be vigilant in the assessment of kidney function in order to provide optimal pharmacotherapy. © National Kidney Foundation, Inc.

- Triantafylidis LK, Hawley CE, Perry LP, Paik JM. The Role of Deprescribing in Older Adults with Chronic Kidney Disease. *Drugs Aging*. 2018 Nov;35(11):973-984.

Older adults with chronic kidney disease (CKD) often experience polypharmacy, a recognized predictor of prescribing problems including inappropriately dosed medications, drug-drug and drug-disease interactions, morbidity and mortality. Polypharmacy is also associated with nonadherence, which leads to recurrent hospitalizations and poorer hemodialysis outcomes in CKD patients. Further complicating medication management in this vulnerable population are the physiologic changes that occur with both age and CKD. This guide for pharmacists and prescribers offers considerations in medication evaluation and management among older adults with CKD. Careful prescribing with the aid of tools such as the American Geriatrics Society Beers Criteria can support safe medication use and appropriate prescribing. Polypharmacy may be systematically addressed through 'deprescribing,' an evidence-based process that enables identification and elimination of unnecessary or inappropriate medications. Detailed guidance for deprescribing in older adults with CKD has not been published previously. We highlight three specific targets for medication optimization and deprescribing in older adults with CKD: (1) proton pump inhibitors, (2) oral hypoglycemic agents, including newer classes of agents, and (3) statins. These medication classes have been chosen as they represent three of the most commonly prescribed classes of medications in the United States. For each area, we review considerations for medication use in older adults with CKD and provide strategies to avoid, modify, or discontinue these medications when clinically indicated. By utilizing deprescribing techniques, pharmacists are well positioned to help decrease the medication burden in older adults with CKD, thereby potentially reducing the risk of morbidity and mortality associated with polypharmacy.



- Wood S, Petty D, Glidewell L, Raynor DT. Application of prescribing recommendations in older people with reduced kidney function: a cross-sectional study in general practice. *Br J Gen Pract*. 2018 May;68(670):e378-e387.

BACKGROUND: Kidney function reduces with age, increasing the risk of harm from increased blood levels of many medicines. Although estimated glomerular filtration rate (eGFR) is reported for prescribing decisions in those aged ≥ 65 years, creatinine clearance (Cockcroft-Gault) gives a more accurate estimate of kidney function. AIM: To explore the extent of prescribing outside recommendations for people aged ≥ 65 years with reduced kidney function in primary care and to assess the impact of using eGFR instead of creatinine clearance to calculate kidney function. DESIGN AND SETTING: A cross-sectional survey of anonymized prescribing data in people aged ≥ 65 years from all 80 general practices (70 900 patients) in a north of England former primary care trust. METHOD: The prevalence of prescribing outside recommendations was analyzed for eight exemplar drugs. Data were collected for age, sex, actual weight, serum creatinine, and eGFR. Kidney function as creatinine clearance (Cockcroft-Gault) was calculated using actual body weight and estimated ideal body weight. RESULTS: Kidney function was too low for recommended prescribing in 4-40% of people aged ≥ 65 years, and in 24-80% of people aged ≥ 85 years despite more than 90% of patients having recent recorded kidney function results. Using eGFR overestimated kidney function for 3-28% of those aged ≥ 65 years, and for 13-58% of those aged ≥ 85 years. Increased age predicted higher odds of having a kidney function estimate too low for recommended prescribing of the study drugs. CONCLUSION: Prescribing recommendations when kidney function is reduced are not applied for many people aged ≥ 65 years in primary care. Using eGFR considerably overestimates kidney function for prescribing and, therefore, creatinine clearance (Cockcroft-Gault) should be assessed when prescribing for these people. Interventions are needed to aid prescribers when kidney function is reduced. © British Journal of General Practice.



Next Month's Issue:

High Risk Medications:
Balancing the Risks and Benefits When Deprescribing

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