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EDITORIAL

Renal Function Assessment and Direct-Acting Oral Anticoagulants Dosing: Are We Entering a New Age?

See Article by Rohla et al

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In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Rohla et al[1] raise concerns regarding the current practice of basing renal dosing adjustments for direct-acting oral anticoagulants (DOACs) in patients with atrial fibrillation (AF) on estimated creatinine clearance (CrCl).[1] Using registry data for patients with AF, they estimated CrCl using the Cockcroft-Gault (CG) formula and glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas; they compared thromboembolic and bleeding complications between patients with dissimilar renal dosing indications using the 3 formulas based on prescribing information in Europe. Nearly 40% of patients would have required dosage adjustment using either the Modification of Diet in Renal Disease or CKD-EPI formulas instead of CG. Importantly, thromboembolic events were 5-fold higher in patients whose DOAC dose would have been adjusted based on reclassification using the CKD-EPI formula compared with the CG formula (4.1% versus 0.8%, P=0.01). Major bleeding events were also numerically greater in patients who were reclassified using the CKD-EPI formula (5.7% versus 2.7%, P=0.09), but the difference was not statistically significant.

Over the last decade, DOACs have surpassed warfarin as the predominant oral anticoagulant used to prevent stroke in patients with AF, accounting for 87% of oral anticoagulant prescriptions for this indication in a recent analysis.[2] Among patients prescribed DOACs for AF, the frequency of CKD is estimated between 11.5% and 44.6%.[2] Importantly, each of the 4 DOACs approved for stroke prevention in AF requires dosage adjustment in the setting of CKD.[3–6] For 3 of these drugs—dabigatran, rivaroxaban, and edoxaban—renal dosing adjustments are based on estimated CrCl, typically calculated using the CG formula.[3,4,6,7]

Originally published in 1976, the CG formula for estimating CrCl has been the standard method used to assess renal function and guide dosing adjustments for renally cleared drugs, such as the DOACs.[7] Using readily available clinical and demographic information—age, sex, weight, and serum creatinine—the CG formula is simple, can be easily calculated, is commonly reported in electronic health records, and often incorporated into clinical decision support systems to alert clinicians of the need to adjust medication dosing due to diminished renal function. In 1998, the Food and Drug Administration provided guidance for the pharmaceutical industry recommending the use of dose adjustment categories for patients with renal impairment based on estimations of CrCl, highlighting the CG formula—but not others—as one of the ways to estimate CrCl.[8]

However, use of the CG formula to assess renal function has some pitfalls. Other methods for estimating renal function exist and may be more accurate in

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estimating GFR.[9,10] Additionally, calculation of CrCl using the CG formula can be nuanced in certain clinical scenarios (eg, obesity, drug-specific CG calculations) potentially leading to inaccurate renal function assessments and improper dosing adjustments. In the case of DOACs, inappropriate dose adjustments based on less accurate estimates of GFR may place patients at risk for thromboembolic and bleeding complications.

Given the nuances associated with renal dosing recommendations for DOACs, it is not surprising that Rohla et al found the use of other formulas to estimate GFR would have led to dosage adjustments in large proportion of patients. Since creatinine excretion is influenced by muscle mass, body habitus, and weight can influence CrCl estimates calculated using the CG formula. Prescribing information in the United States for rivaroxaban specifies the use of total body weight when estimating CrCl while the use of total body weight is implied in the prescribing information for edoxaban, which specifies use of the CG formula.[4,6] Cockcroft and Gault[7] acknowledged that body habitus (eg, less muscle mass) and weight extremes (eg, marked obesity) can lead to inaccurate estimates of CrCl. For example, in obese patients, CrCl can be significantly overestimated when using total body weight in CG formula and underestimated when ideal body weight is used, potentially leading to inappropriate dose adjustments of DOACs. Interestingly, Lucijanic et al[11] found a direct relationship between body mass index and both thromboembolic and bleeding complications in patients treated with DOACs. No association was found between estimated GFR, calculated using the Modification of Diet in Renal Disease formula which does not incorporate weight, and clinical outcomes; associations with CrCl were not evaluated.[11] In overweight, obese, and morbidly obese patients, studies have suggested the most accurate estimate of CrCl is obtained using either lean or adjusted body weight when using the CG formula.[12,13] However, doing so conflicts with prescribing information for rivaroxaban and edoxaban and may lead to dosing irregularities. Rohla et al[1] used total body weight in their calculation of CrCl which may overestimate CrCl in overweight and obese patients when using the CG formula. Although they did not report weight, the mean body mass index (28.0±4.8 kg/m^2) was indicative of an overweight population for whom an adjusted body weight may have been more accurate.[1]

In contrast to dabigatran, rivaroxaban, and edoxaban, apixaban-dose adjustments are not based on an estimated CrCl but rather a combination of age, weight, and serum creatinine.[5] The apixaban dose should be reduced when any 2 of the following criteria are met: age ≥80 years, total body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.[5] Because apixaban-dose adjustments in the United States are not based on estimates of CrCl, it may be preferred to other DOACs in patients for whom estimates of CrCl may be inaccurate, such as weight extremes, until there is agreement on the optimal—and practical—method to guide DOAC renal dosing adjustments.

Looking forward, it may be time to re-evaluate using the CG formula as the standard to estimate CrCl and guide renal dosing adjustments for DOACs.[14] Given that the Modification of Diet in Renal Disease and CKD-EPI formulas have been shown to be more accurate estimates of GFR than the CG formula, scientists within both the academic community and pharmaceutical industry should evaluate whether the use of alternatives to the CG formula to estimate GFR and guide renal dosing of DOACs optimize their pharmacokinetics, pharmacodynamics, effectiveness, and safety as the observations of Rohla et al suggest. Furthermore, if such analyses lead to improved patient outcomes, the Food and Drug Administration should strongly consider updating renal dosing recommendations for DOACs to include the use of alternative formulas to estimate GFR.

It is possible, if not likely, that a one-size-fits-all approach to assessing renal function and making renal dosing adjustments (eg, use of the CG formula) is no longer sufficient—both for DOACs and other renally cleared drugs, particularly those with narrow therapeutic windows between safety and efficacy. There is evidence in other settings (eg, platin-based chemotherapy, vancomycin, etc) that using estimated GFR (calculated from alternative formulas) rather than CrCl (calculated from the CG formula) can guide treatment decisions, optimize dosing, and predict adverse outcomes.[14] As with DOACs, academic scientists, the pharmaceutical industry, and the Food and Drug Administration should evaluate whether these formulas optimize dosing of renally cleared drugs and incorporate them into renal dosing recommendations if studies validate GFR-based renal dosing adjustments similar to what Rohla et describe herein.[1] Then we will be able to turn the page from CG formula.

In the meantime, the association between misclassification of renal dosing adjustments of DOACs with an increased risk of thromboembolic events reinforces the importance of critically evaluating renal function and thoughtfully adjusting DOAC doses. One of the main advantages of DOACs is their diminished need for routine monitoring compared with the intensive monitoring of the International Normalized Ratio required with warfarin. However, assessment of renal function at baseline and regularly throughout the course of therapy is warranted. Utilization of anticoagulation clinics, typically managed by clinical practitioners other than physicians, to monitor renal function at predetermined intervals and make necessary dosing adjustments has been suggested.[15] Given the events of the COVID-19 pandemic, the concept of virtual anticoagulation clinics (eg, anticoagulation cloud) may feasibly increase our vigilance in monitoring renal function and making necessary dosing adjustments in patients treated with DOACs.[15] Pharmacists are often part of the anticoagulation team, understand the pitfalls associated

with the CG formula, and can provide pragmatic renal dosing recommendations for DOACs when uncertainty arises.

ARTICLE INFORMATION

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