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EDITORIAL COMMENT

Which Renal Function Equation Should Be Used for Prescribing DOACs in Patients With Atrial Fibrillation?*

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Globally, atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults, with an estimated prevalence of 2%-4%.[1] AF is associated with increased morbidity and mortality, posing heavy burden to patients, physicians, and health care systems worldwide. In previous pivotal randomized clinical trials (RCTs), direct oral anticoagulants (DOACs) have shown noninferiority to warfarin in the prevention of stroke/systemic embolism.[2-5] In a meta-analysis of these RCTs, DOACs showed a favorable risk-benefit profile with a 19% significant reduction in stroke/systemic embolic events, a 51% reduction in hemorrhagic stroke, and a 10% reduction in all-cause mortality with similar major bleeding risk reduction as warfarin.[6] Current American and European guidelines on the management of AF recommend the use of DOACs in preference to warfarin for secondary prevention in patients with nonvalvular AF in most clinical scenarios.[7,8]

Considering that inappropriate dosage of DOACs would attenuate the advantages of DOAC treatment compared to warfarin, it is necessary to adjust the dosage of DOACs based on the patient's renal function. In previous pivotal RCTs, the Cockcroft-Gault (CG) formula (which uses patient's age, sex, and body weight) was most frequently used to estimate the renal function of patients with AF.[9] However, in routine clinical practice, the estimated glomerular filtration rates (eGFRs) of AF patients are commonly estimated based on the Modified Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, as these 2 formulae do not require the inclusion of information about patient' body weight. The eGFRs based on the MRDR or CKD-EPI formula are reported automatically in many laboratories, and may be relatively more user-friendly and convenient for daily clinical practice. However, data about differences between eGFRs calculated using different equations and the impacts of the different eGFR equations on the dosage selections of DOACs and subsequent clinical outcomes are limited.

In this issue of *JACC: Asia*, Chan et al[10] present a unique study to investigate the agreements/disagreements of eGFRs calculated using different equations (CG formula as a reference vs MDRD formula and CKD-EPI formula) in Asian patients with AF; they evaluate the impacts of using different equations on the dosage (underdosing, on-label dosing, or hyperdosing) of DOACs used and assess the clinical outcomes (including mortality, major bleeding, and ischemic stroke/systemic embolism) compared with warfarin. The study was a large-scale retrospective analysis of patients' electronic records from the Chang Gung Memorial Hospital (CGMH) medical system. The mean age of the study population was 71.1 ± 12.8 years and 57% were males. Chan et al[10] found that, compared to the CG equation, the adoptions of the MDRD or the CKD-EPI equation would overestimate eGFRs in a considerable percentage of AF patients, especially for patients ≥75 years of age with body weight <50 kg, and would result in inappropriate dosage of DOACs (mainly overdosing), which

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would attenuate the benefits of DOACs compared to warfarin. Therefore, the CG equation should be used as the "gold standard" for calculating eGFRs to guide the optimal DOACs dosages of AF patients in routine clinical practice.

Their findings provide valuable information on the choice of formula for calculating eGFRs of AF patients to guide the DOAC dosage in the clinical practice, in particular for elderly and lower-body-weight patients with AF in Asia. However, the results from this study must be interpreted in the context of the following limitations.

First, this study was a retrospective observational study based on the electronic medical record database, which recruited only AF patients who were admitted to the hospital. There was no information on patients who experienced adverse events outside the CGMH medical system, which could cause potential selection bias. In addition, although some baseline differences were adjusted in the regression model in this study, residual measured and unmeasurable confounders may still have contributed to some of these results.

Second, it was unclear whether the results of this study were consistent among patients without data for serum creatinine (sCr). As a retrospective analysis of medical records, there was no universal and prespecified algorithm for assessing levels of sCr in patients with AF in this study. Of the 70,408 initially recruited patients, just 39,239 were analyzed after excluding patients with missing data of body weight and sCr.

Third, because this study focused on Taiwanese AF patients from the CGMH medical system, it is unclear whether these findings are generalizable to other populations in other areas with different racial/ethnic composition, practice patterns, and health care systems. Asian patients with AF are generally leaner compared to European and North American AF patients. Because lower body weight is significantly associated with the possibility of overestimation of eGFRs, the overestimations of eGFRs with MDRD and CKD-EPI equations may be more evident among Asian AF patients than Caucasian AF patients.

Finally, although there is inconsistency in eGFRs calculated using different renal formulae in clinical practice, the actual impact caused by this inconsistency on the dosage of DOACs is not significant. In fact, the reference criterion for determining the dosage of DOACs used is not only based on the patient's renal function. Furthermore, it is common to use DOACs at a reduced dosage in daily clinical practice in Asia even among patients who do not meet the criteria of dosage reduction.[11] However, considering that the inappropriate dosage of DOACs would diminish the benefits of treatment, the CG equation should be used as the gold standard for the calculations of eGFRs to guide the DOACs dosages.

In summary, the investigators have provided valuable evidence of real-world study on the choice of renal function estimation formula for determining the dosage of DOACs in patients with AF. The adoptions of MDRD or CKD-EPI equations instead of the CG equation would result in inappropriate dosage of DOACs (mainly overdosing) which would attenuate the benefits of DOACs compared to warfarin. In the routine clinical practice, the CG equation should be regarded as the gold standard for calculating eGFRs to guide the optimal dosage of DOACs for patients with AF in Asia.

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