Renal Function Estimates and Dosing of Direct Oral Anticoagulants in Stroke Patients with Atrial Fibrillation: An Observational Study

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Abtract

Purpose: Appropriate dosing of direct oral anticoagulants (DOACs) requires consideration of renal function. Discordance between commonly used estimated glomerular filtration rate (eGFR) and creatinine clearance (CrCl) might affect the dosing appropriateness in stroke patients with atrial fibrillation (AF). We aimed to explore the effect of renal function estimates on the dosing patterns in a real-world setting.

Methods: Using a hospital-based stroke registry, we identified consecutive patients between 2014 and 2017 who were hospitalized for acute stroke, had AF, and started DOACs within 90 days after stroke. We compared the difference between eGFR and CrCl in assessing appropriateness of dosage. Effectiveness and safety outcomes were verified by chart review, and event rates were presented as per 100 person-years.

Results: Of the156 patients with mean age 74±11 years, 72 (46%) were prescribed dabigatran and 84 (54%) rivaroxaban. Substituting eGFR for CrCl would have 55% (37/67) of patients with CrCl <50 mL/min and 89% (8/9) of patients with CrCl <30 mL/min not correctly classified, and potentially lead to overdosing. The misclassification would cause underdosing in 6% (5/89) of patients with CrCl ≥50 mL/min and 1% (1/147) of patients with CrCl ≥30 mL/min. In reality, the substitution resulted in reduction of overdosing from 10% to 4% for dabigatran and from 2% to 1% for rivaroxaban; underdosing increased from 17% to 26% for rivaroxaban. After median follow-up of 17 months, 33 patients developed outcomes including 21 major bleedings. The event rate was 6.9% per year (95% CI, 4.1%-11.4%) for effectiveness, and 9.6% per year (95% CI, 6.3%-14.8%) for safety.

Conclusion: Although substituting eGFR for CrCl carries potential risks of DOAC overdosing in patients with AF, the effect might be offset by clinicians' predilection for lower dosage in this stroke cohort.

Key words: Stroke; atrial fibrillation; direct oral anticoagulant; creatinine clearance; Cockcroft-Gault; glomerular filtration rate; Modification of Diet in Renal Disease

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INTRODUCTION

Direct oral anticoagulants (DOACs) are the mainstream treatment for embolic prevention in patients with nonvalvular atrial fibrillation (AF). Optimal dosing of DOACs requires consideration of renal function. Most of the DOAC randomized clinical trials (dabigatran, rivaroxaban, edoxaban) used creatinine clearance (CrCl) with the Cockcroft-Gault (CG) formula to estimate renal function[1-3]. In clinical practice, estimated glomerular filtration rate with the Modification of Diet in Renal Disease equation (eGFR-MDRD) is readily available to clinicians because the calculation does not need body weight input[4]. A study reported that substituting eGFR for CrCl could fail to recognize the need for dose reduction in substantial proportions of patients and thus potentially affect the safety of medication[5]. This concern is particularly important for stroke patients with AF because they carry higher risk of major bleeding while on DOACs for secondary prevention. On the other hand, clinicians in Asian countries reportedly tend to prescribe low doses of DOACs in fear of bleeding complications[6]. It is not clear that under such prescription preferences what magnitude of impact the discordance between CrCl and eGFR would play on the appropriate dosing of DOACs in real-world clinical practice.

Using a hospital-based stroke registry in Taiwan, we aimed to explore how the DOAC dosage could be affected if eGFR-MDRD estimate was used in place of CrCl in patients with AF after acute stroke.

METHODS

The study cohort was assembled from a stroke registry in the Chi-Mei Medical Center, a teaching hospital with more than 1,200 beds and a participant of the nationwide Taiwan Stroke Registry[7]. In brief, the registry prospectively enrolled consecutive patients who presented to hospital within 10 days after stroke onset. Patient characteristics, including demographic data, medical history, comorbidity, stroke severity, treatments, hospital course, and complications, were collected according to a pre-defined system. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS), and functional status was categorized with the modified Rankin Scale. For the present study, we identified acute stroke patients who were hospitalized between January 2014 and December 2017, had an electrocardiography and echocardiography-documented nonvalvular AF, and started a DOAC within 90 days after onset of the index stroke. Because only two DOACs were available in this hospital before October 2017 (specifically, dabigatran 110/150 mg and rivaroxaban 10/15/20 mg), the few patients who were prescribed with other DOACs after October 2017 were not included.

For the exploratory purpose, we only focused on renal function and did not consider other factors for recommended dosage adjustment. In each patient we calculated CrCl-CG (eCrCl (mL/min) = (140-age) × weight (kg)/72 × creatinine (mg/dL) (× 0.85 if women)), and eGFR-MDRD (eGFR (mL/min/1.73 m^2) = 175 × (creatinine (mg/dL))$^{-1.154}$ × (Age)$^{-0.203}$ (× 0.742 if women) [4,8]. We then compared the discrepancy between the two estimates at the threshold levels of 30 mL/min and 50 mL/min under which either dabigatran or rivaroxaban is recommended for dose reduction. The true starting date and the dosage of DOAC were extracted by medical chart review. The appropriateness of DOAC dosing based on renal function was determined according to the manufacturer labelling approved by the Taiwan Food and Drug Administration ((HYPERLINK "http://www.fda.gov.tw/mlms/ShowFile.aspx?LicId=02025458&Seq=005&Type=9"www.fda.gov.tw/mlms/ShowFile.aspx?LicId=02025458&Seq=005&Type=9; www.fda.gov.tw/mlms/ShowFile.aspx?LicId=02025647&Seq=009&Type=9).

We traced the follow-up course of each patient until the last record in our medical care network, which included additional two affiliated hospitals. The medical records of re-hospitalization were independently reviewed by the two study neurologists. The effectiveness outcome was a composite endpoint of recurrent stroke (ischemic or hemorrhagic), systemic embolism, acute myocardial infarction, and death from any cardiovascular causes. The safety outcome was a composite of major bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site, a fall in hemoglobin concentration >2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability. The research proposal had been approved by the study hospital's Institutional Review Board.

Data were presented as mean or median for numerical variables, and proportion for categorical variables as appropriate. We calculated event rates for effectiveness outcome and safety outcome per 100 patient-years. Data analysis was performed using STATA 12 (StataCorp, College Station, Texas).

RESULTS

A total of 156 stroke patients with AF were included for analysis. The clinical characteristics are displayed in Table 1. In general, this group consisted of elderly patients with mild to moderate stroke severity (median admission NIHSS 4, interquartile range [IQR], 2-12). The mean CHADS2 score was 3.6±0.8 (median 4, IQR 3-4). The correlation between the two renal function estimates is illustrated in the Figure, with highlights of levels at 30 and 50 mL/min which are recommended thresholds for dose adjustment of either DOAC. No patient had a renal function estimate <15 mL/min, a level that DOACs are not recommended to use. Substituting eGFR-MDRD for CrCl resulted in potential misclassification. Specifically, 55% (37/67) of patients with CrCl < 50 mL/min would not have been correctly classified, and 89% (8/9) of patients with CrCl < 30 mL/min would have been classified otherwise. Meanwhile, 6% (5/89) of patients with CrCl≥50 mL/min would have been incorrectly classified, and misclassification occurred in 1% (1/147) of patients with CrCl≥30 mL/min. Overall, 29% (45/156) of patients could have been overdosing, and 0.4% (6/156) underdosing.

In actual practice, 72 (46%) of patients were prescribed dabigatran and 84 (54%) rivaroxaban. Around three-fourths of the patients started a DOAC within 30 days after stroke onset. As shown in Table 2, if CrCl-CG had been considered in clinical practice, 10% (7/72) of patients on dabigatran were overdosing and none were underdosing, whereas 2% (2/84) of patients on rivaroxaban were overdosing and 17% (14/84) were underdosing. If eGFR-MDRD had been used instead, overdosing occurred in 4% (3/72) of patients on dabigatran and none were

Table 1. Clinical characteristics of 156 stroke patients with atrial fibrillation.

Age, mean (SD), year	74 (11)
Male, n (%)	84 (54)
Body mass index, mean (SD), kg/m^2	24.4 (4.5), 1 missing
Weight, mean (SD), Kg	64 (13)
Hypertension, n (%)	117 (75)
Diabetes mellitus, n (%)	44 (28)
Hyperlipidemia, n (%)	113 (72)
Previous stroke or TIA, n (%)	45 (29)
Ischemic heart disease, n (%)	29 (19)
Heart failure	13 (8)
Smoking, n (%)	45 (29)
Pre-stroke mRS, median [IQR]	0 [0-2]
NIHSS at admission, median [IQR]	4 [2-12]
$CHADS_2$ score, mean (SD)	3.6 (0.8)
Creatinine, median [IQR] (range), mg/dL	0.96 [0.78-1.22] (0.54-2.63)
CrCl-CG, median [IQR] (range), mL/min	54 [41-67] (17-143)
GFR-MDRD, median [IQR] (range), mL/min/1.73 m^2	67 [52-81] (24-128)
Length of stay, median [IQR], day	8 [4-15]
Initiation of DOAC after stroke, median [IQR], day	17 [9-32]
Discharge mRS, median [IQR]	2 [1-4]

SD: standard deviation; IQR: interquartile range; TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale; CrCl-CG: creatinine clearance by the Cockcroft-Gault equation; GFR-MDRD: glomerular filtration rate by the Modification of Diet in Renal Disease equation; DOAC: direct oral anticoagulant; mRS: modified Rankin Scale.

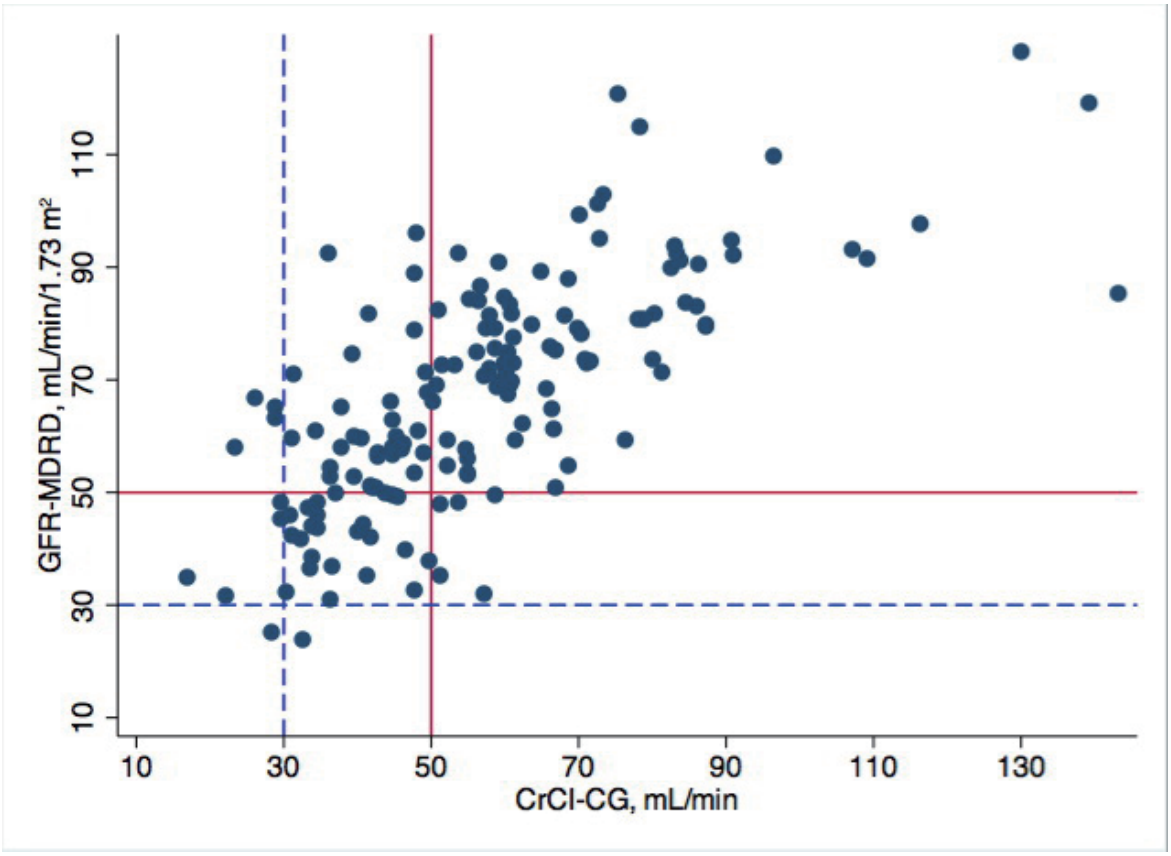

Figure. Comparison of creatinine clearance by the Cockcroft-Gault equation (CrCl-CG) and glomerular filtration rate by the Modification of Diet in Renal Disease equation (GFR-MDRD) at the threshold levels for dose adjustment of direct oral anticoagulants in 156 stroke patients with atrial fibrillation.

Table 2. Appropriateness of DOAC dosing by renal function estimate of eGFR-MDRD or CrCl-CG (in parentheses) among 156 stroke patients with atrial fibrillation.

	Dabigatran, n=72			Rivaroxaban, n=84			
Renal function estimate by eGFR-MDRD (By CrCl-CG)	Manufacturer labelling for dose adjustment	110 mg BD	150 mg BD	Manufacturer labelling for dose adjustment	10 mg OD	15 mg OD	20 mg OD
<15	Not recommended	0 (0)	0 (0)	Not recommended	0 (0)	0 (0)	0 (0)
15~29	Not recommended	0 (3*)	1* (1*)	10 or15 mg OD	0 (3)	1 (2)	0 (0)
30~49	110 mg BD	14 (19)	2* (3*)	10 or 15 mg OD	8 (13)	8 (21)	1* (2*)
≥50	150 or 110 mg BD	43 (35)	12 (11)	15 or 20 mg OD	22# (14#)	40 (26)	4 (3)
Total		57	15		30	49	5

*Overdose; #Underdose.

Data are number of patients.

DOAC: direct oral anticoagulant; CrCl-CG: creatinine clearance by the Cockcroft-Gault equation, mL/min; eGFR-MDRD: estimated glomerular filtration rate by the Modification of Diet in Renal Disease equation, mL/min/1.73 m^2

Table 3. Effectiveness and safety outcomes among 156 stroke patients with atrial fibrillation and taking direct oral anticoagulants

	Number	Event rate, per 100 patient-years (95% confidence interval)
Effectiveness composite endpoint	15	6.9 (4.1 - 11.4)
Stroke*	11	
Systemic embolism	1	
Acute myocardial infarction	1	
Death from cardiovascular causes	2	
Safety endpoint	21	9.6 (6.3 - 14.8)
Bleeding with hemoglobin fall >2 g/dL, or blood transfusion > 2 units	10	
Bleeding hemoglobin fall >4 g/dL, or blood transfusion> 4 units	5	
Intracranial hemorrhage	5	
Other critical site bleeding	1	

*Hemorrhagic strokes (n=3) were included in both the effectiveness and safety endpoints.

underdosing, whereas 1% (1/84) of patients on rivaroxaban were overdosing and 26% (22/84) underdosing.

After a median follow-up of 17 (IQR 10-27) months, 33 patients developed outcomes of interest (Table 3). Effectiveness composite endpoint occurred in 15 patients, an incidence rate being 6.9% per year (95% confidence [CI], 4.1%-11.4%). Twenty-one patients had safety composite outcomes, an incidence rate being 9.6% per year (95% CI, 6.3% - 14.8%).

DISCUSSION

In this stroke cohort with AF, theoretically 55% of patients with CrCl-CG <50 mL/min and 89% of those with CrCl-CG < 30 mL/min could have had overdosing of DOACs if eGFR-MDRD was used instead. In reality, clinicians' prescription preference alleviated the potential overdoing and intensified the potential underdosing. Specifically, the overall proportion of overdosing reduced from 10% to 4% for dabigatran, and from 2% to 1% for rivaroxaban. The proportion of underdosing increased from 17% to 26% for rivaroxaban.

The roles of age and body weight in discordance between eGFR-MDRD and CrCl are documented.5 Our results confirm that those who are older or weighed less have higher eGFR than CrCl-CG. Furthermore, Schwartz reported that substituting eGFR-MDRD for CrCl would potentially result in failure to recognize indications for reducing DOAC doses in 28% of the National Health and Nutrition Examination Survey sample (mean age 46 years) at the cutoff level of < 50 mL/min and 21% at the cutoff level < 30 mL/min. The corresponding numbers were 56% and 86% of the research sample (mean age 68 years) respectively[5]. Our results were more close to those in the research sample, probably because our patients were older as well.

In real-world practice, clinicians' preference for dose reduction was more apparent for rivaroxaban than for dabigatran in our patients. Prior research using the Taiwan National Health Insurance Research Database reported that in Taiwanese AF patients treated with DOACs, around 90% were taking low doses of dabigatran or rivaroxaban[6]. The claims data do not contain laboratory workup and thus dosage could not be correlated with renal function. With available renal function measurements, our study revealed a consistent dose-reduction practice pattern in this stroke cohort. Therefore even though substituting eGFR-MDRD for CrCl potentially would lead to overdosing, the magnitude seemed offset by the low-dose prescription preference. On the contrary, the substitution of eGFR-MDRD for CrCl might exaggerate the prevalence of dose reduction. Among our study patients, this situation was particularly notable for rivaroxaban. In routine clinical practice, prescribed DOAC doses are often inconsistent with drug labeling[9,10]. We demonstrated that it is warrant to note the discrepancy between different renal function

estimates.

Our cohort, consisting of acute stroke patients with atrial fibrillation, were at moderate risks of further embolism in light of the mean $CHADS_2$ score (3.6±0.8). The effectiveness event rate (6.9% per year) and major bleeding rate (9.6% per year) were higher than those in the randomized clinical trials (1.1% to 2.1% and 2.7% to 3.6%, respectively)[1,2]. Underdosing of DOAC could not explain the higher bleeding rate. It was probable that our stroke patients had worse functional disability and other medical comorbidities, and thus carried high risk both for the effectiveness and safety outcomes. Additionally, the sample size was too small to adjust for potential risk factors for outcome events.

The strength of our study was that the prospective systematic registry contained important characteristics of stroke and adequate data for calculating both renal function estimates. This study has some limitations. First, study of a hospital-based registry data might restrict the generalizability of our findings. Second, other factors for dose adjustment such as liver function and concomitant medications were not considered. Thus the determination of dosage appropriateness might not be reliably ascertained. Third, the continuity of prescription and the adherence of patients were not evaluated, and the medical records outside of the hospital system were not available. Therefore the effectiveness and safety event rates relevant to DOACs might be over- or underestimated. Forth, because of the small sample size, we were not able to compare the outcomes between the misclassified renal function group and the correctly classified renal function group in this study. Even with these limitations, our study pointed out an important clinical issue for clinicians to consider when prescribing DOAC for stroke patients with AF.

In conclusion, although substitution of eGFR-MDRD for CrCl-CG, which randomized trials and drug labelling are based on, carries potential risks of DOAC overdosing, the effect might be offset by clinicians' predilection for prescribing lower doses in this high-risk stroke cohort in Taiwan.

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