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Evaluation of DOAC Dosing Among Various Renal Equations in Patients With Kidney Impairment and Elderly in Thailand

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ABSTRACT

The Thai Food and Drug Administration (TFDA) has approved direct oral anticoagulant (DOAC) dosing based on estimated creatinine clearance, eCrCl (Cockcroft-Gault equation). However, other renal function equations are often used in practice for patients with kidney disease, leading to potential discrepancies in DOAC dosing recommendations. The actual DOAC dosing patterns in resource-limited countries remain underreported. This cross-sectional study included patients with renal impairment who were treated at the outpatient department of Siriraj Hospital, Mahidol University, Thailand. Patients received their first DOAC for atrial fibrillation from January 2019 to December 2022. The primary objective was to evaluate the percentage of DOAC prescriptions compliant with TFDA guidelines using eCrCl. We also examined dosing agreement when substituting estimated glomerular filtration rate, eGFR (CKD-EPI) for eCrCl. Patient factors and the incidence of stroke and bleeding over a one-year follow-up were also assessed. A total of 326 patients and 1587 DOAC prescriptions were analyzed. The mean patient age was 79.1 ± 9.2 years, with a mean eGFR of 45.6 ± 9.9 mL/min/1.73 m^2. TFDA-compliant dosing was observed in 68.2% of prescriptions. Dose disagreement between eGFR and eCrCl was 45%, with a trend toward overdosing using eGFR. An eGFR of less than 45 mL/min/1.73 m^2 was associated with dose discrepancies. Stroke and bleeding incidences were low, with no differences across DOAC types. While most Thai patients received appropriate DOAC dosing, one-third did not comply with TFDA guidelines. Using eGFR instead of eCrCl may result in dosing differences, particularly in moderate to severe renal impairment.

1 | Introduction

Elderly patients with chronic kidney disease (CKD) face a significantly elevated risk of developing atrial fibrillation (AF) [1, 2]. Direct oral anticoagulants (DOACs) play a crucial role in managing AF, particularly for CKD stages 1–4, due to their improved efficacy and safety advantages [2]. However, optimizing DOAC dosing in real-world practice remains challenging because it requires adjustments based on kidney function. Current product information for all DOACs recommends using estimated creatinine clearance (eCrCl) by the Cockcroft-Gault (C-G) equation for dose adjustments. However, the recently released 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines propose an alternative approach using estimated glomerular filtration rate (eGFR) derived from serum creatinine for drug dosing [2]. This aligns with the growing use

Summary

- What is the current knowledge on the topic?
  - Direct oral anticoagulants (DOACs) need dosage adjustments according to kidney function and other factors.
- What question did this study address?
  - The percentage of real DOAC prescribing corresponds to DOAC dosing recommendations followed by eCrCl (C-G equation). The proposed reasons for non-compliance with dosing include other renal equations used (eGFR by CKD-EPI), the degree of kidney function, and other criteria for DOAC dosing consideration.
- What does this study add to our knowledge?
  - The study of Thai elderly patients with kidney impairment receiving DOACs for AF found that one-third of DOAC prescriptions did not comply with Thai FDA labels.
  - Over-dosing of DOACs might arise from differences in eGFR (CKD-EPI) and eCrCl (C-G), with the former being of greater value in patients with moderate kidney impairment. The cut-off eGFR value that should be recalculated to eCrCl is less than 45 mL/min/1.73 m^2 because it is associated with dose discordance between renal equations found in our study.
  - Under-dosing of apixaban occurred because most patients did not meet the patient factor criteria for drug dosing in the recommendations.
- How might this change clinical pharmacology or translational science?
  - Using other renal equations besides the recommendations may not be problematic if patients have normal kidney function. However, patients with moderate to severe kidney dysfunction should use the approved kidney function due to the differences in dosing between renal equations.
  - Our study, conducted in a resource-limited country, still supports renal equations according to product-approved dosing.

of eGFR via the CKD-EPI formula in routine clinical settings to diagnose and stage CKD [2, 3]. As a result, some healthcare providers are using auto-reported eGFR (based on CKD-EPI) to guide DOAC dosing, raising questions about its equivalence to the standard eCrCl. Inconsistencies in DOAC dosing strategies can potentially impact both treatment effectiveness and bleeding risks.

Several landmark studies have proven the efficacy of DOACs for AF patients, conducted in Western countries [4–7]. While patient characteristics among various populations may influence AF clinical outcomes, a higher proportion of Asian patients with AF are very elderly (defined as over 75 years) and have low body weight compared with non-Asian patients [8]. Elderly patients with AF have both stroke and bleeding risks, which have been found to have a high incidence in Asian populations [9]. A recent study of the Thai population found that inappropriate DOAC dosing may pose a risk for thromboembolic complications and bleeding if the dosage is too low or too high, respectively [10]. When estimating kidney function using some renal equations, such as the Modification of Diet in Renal Disease (MDRD) [11] or CKD-EPI [12], race is a contributing factor associated with different values of renal function estimation. As dosing guidance for DOACs in Asian patients is still lacking, DOAC dosing studies from specific Asian populations should be encouraged for better implementation for Asian patients.

This study aimed to evaluate the proportion of DOAC prescriptions in Thailand that adhere to the dosing recommendations established by the Thai Food and Drug Administration (TFDA), which are based on eCrCl. The prevalence of utilizing eGFR (CKD-EPI) as a surrogate for dosage adjustment in real-world DOAC prescribing was explored. We also considered the influence of factors beyond renal function, as outlined by the TFDA guidelines, on DOAC dosing decisions. The findings from this study offer a valuable illustration of DOAC prescribing patterns within a resource-constrained setting. These insights can be extrapolated to other healthcare contexts with similar characteristics, potentially informing the optimization of clinical practice in such settings.

2 | Materials and Methods

2.1 | Study Setting

Siriraj Hospital is a leading tertiary care, university-affiliated hospital in Thailand with a multidisciplinary care approach in the outpatient setting. We captured all DOAC prescriptions regardless of the facility or office location in the outpatient setting. Our policy requires that when patients have serum creatinine measured, eGFR by the CKD-EPI equation (2012) is automatically reported, in compliance with recommendations from the KDIGO guideline [2] and the national Thai CKD guideline [3].

2.2 | Study Design

This cross-sectional study included patients from the outpatient department at Siriraj Hospital, Mahidol University. The inclusion criteria were: (1) males or females aged ≥18 years, (2) patients with kidney impairment defined as eGFR <60 mL/min/1.73 m^2 or those diagnosed with CKD, and (3) patients receiving their first DOAC for AF between January 1, 2019, and December 31, 2022. Four DOACs were available in the hospital during the study period: apixaban, dabigatran, edoxaban, and rivaroxaban. We excluded patients who were on dialysis and kidney transplantation at baseline. Patients who did not have sufficient information to evaluate kidney function within 3 months before starting DOAC, or who were lost to follow-up within 1 year after receiving the first DOAC were also excluded from the study.

The sample size calculation was determined by the formula: $N = [Z^2\alpha/2 \times P\ (1\text{-}P)]/M^2$, where Z represents the Z statistic for a 95% confidence level, P is the proportion of patients who did not receive appropriate DOAC dosing (0.295 based on a study by Ting C, et al.) [13], and M is the margin of error (0.05). Based on this formula, a minimum sample size of 320 patients was

calculated. To account for potential loss of follow-up, estimated at 5%, the sample size was adjusted. Therefore, the required number of patients ranged from 320 to 336 to ensure the robustness of our results despite potential data loss.

2.3 | Ethics Statement

This study protocol was approved by Mahidol University Multi-Faculty Cooperative IRB Review, Siriraj Institutional Review Board, Siriraj Hospital, Mahidol University, Thailand (MU-MOU 874/2565 (IRB4)). The study was also registered and approved by the Thai Clinical Trials Registry (TCTR20230703002). This study was solely a retrospective review of data gathered from electronic medical records based on routine service. Therefore, formal consent from individual patients was not required.

2.4 | Data Collection

We administered a structured patient information record to each study participant to collect demographic data and relevant clinical history related to DOAC prescribing and medication review. The participant's clinical information, such as age, gender, body weight, kidney function (serum creatinine, eGFR), and complete blood count, was reviewed. Information on DOAC use, including the name, dosage regimen, and drugs that can interact with DOACs, was collected. The investigators also gathered details on the participant's history of antithrombotic agents, NSAID/corticosteroid use, and medications for gastrointestinal (GI) ulcer prevention based on medical records and medication databases. Clinical outcomes were evaluated during the follow-up period, including the incidence of stroke and bleeding noted in the medical charts of the hospital. We thoroughly reviewed both outpatient clinic and inpatient hospitalization records for patients admitted during the study period to identify and account for any changes in DOAC dosing due to efficacy or safety concerns.

The primary outcome was the percentage of DOAC dosages compliant with the TFDA when using creatinine clearance (eCrCl) by C-G as the kidney function assessment. The formula for the C-G equation was (140—age) × ideal body weight [IBW]/72× serum creatinine, with a correction factor of 0.85 for females. We classified the outcomes into three categories: correct dosing, overdosing, and underdosing. DOAC dosage considerations extend beyond kidney function and include factors such as age, body weight, and drug interactions, as outlined in each DOAC's prescribing information. Overdosing was defined as a prescribed dose exceeding the TFDA recommendation, while underdosing referred to a dose below the recommended level. The TFDA-recommended DOAC dosing guidelines are provided in the Supporting Information [14–17].

We also explored whether other renal equations or potential factors are associated with not-approved DOAC dosing. The mean differences in kidney function calculated from eGFR compared with eCrCl were evaluated. The percentages of prescribed doses that complied with TFDA when substituting eGFR with CKD-EPI (mL/min/1.73 m^2) and CKD-EPI non-indexed for BSA (mL/min) for eCrCl were also analyzed in the study. CKD-EPI was calculated by $eGFR = 141\ X_{min}(Cr/\kappa,1)^{\alpha}\ X_{max}(Cr/\kappa,1)^{-1.209}\ X\ (0.993^{Age})\ X\ 1.018$ [if female], where Cr is serum creatinine in mg/dL, κ is 0.7 for females, 0.9 for males, and α is −0.329 for females and −0.411 for males [12]. CKD-EPI non-indexed for BSA can be obtained by multiplying the indexed GFR results by the person's BSA and dividing by 1.73 m^2.

Dosing agreement was defined as the eGFR (by CKD-EPI or CKD-EPI non-indexed for BSA) and the eCrCl recommending the same DOAC dosing based on TFDA recommendations (e.g., both equations recommending full-dose therapy or both equations recommending dose reduction). Over-dosing was defined when the eGFR provided a higher dose than the eCrCl equation, leading to the patient being deemed inappropriately overdosed based on TFDA recommendations. The reverse was defined as under-dosing.

The incidence of adverse clinical outcomes, including stroke and bleeding, was reported during the one-year follow-up after first DOAC prescribing. Clinical bleeding was classified into two categories: clinically relevant non-major bleeding and major bleeding, as defined by The International Society of Thrombosis and Hemostasis (ISTH) [18].

2.5 | Data Analysis

Baseline patient characteristics, information regarding kidney function, and details on drug therapies were analyzed using descriptive analysis. Continuous data were presented as mean ± SD or median and range. Dichotomous data were presented as rates and percentages. Differences were examined using the Paired Samples Test or the Wilcoxon signed-rank test, as appropriate. A significance level of $p < 0.05$ was used to determine statistical significance. The 95% confidence interval for percent agreement, over-dosing, and under-dosing was calculated based on the McNemar-Bowker test. Pre-defined sensitivity analyses were also conducted to identify the threshold kidney function cut-off point to define inconsistencies between the standard eCrCl and eGFR. Data analyses were performed using IBM SPSS Statistics Version 18.

3 | Results

During the study period, 2588 patients received their first DOAC from the outpatient department at the investigation hospital. Among them, 2262 patients were excluded due to not meeting the pre-defined kidney impairment criteria ($n = 1493$), insufficient information for the evaluation of kidney function ($n = 541$), loss to follow-up after 1 year ($n = 213$), and patients receiving DOACs for other indications ($n = 15$). Consequently, 326 patients were included, providing sufficient statistical power for the study, and a total of 1587 DOAC prescriptions were analyzed during the study period. Most patients received apixaban (37.1%), followed by rivaroxaban (25.2%), edoxaban (23.9%), and dabigatran (13.8%), respectively. The study flowchart is presented in Figure 1. The patients had a mean age of 79.1 ± 9.2 years, with a mean eGFR

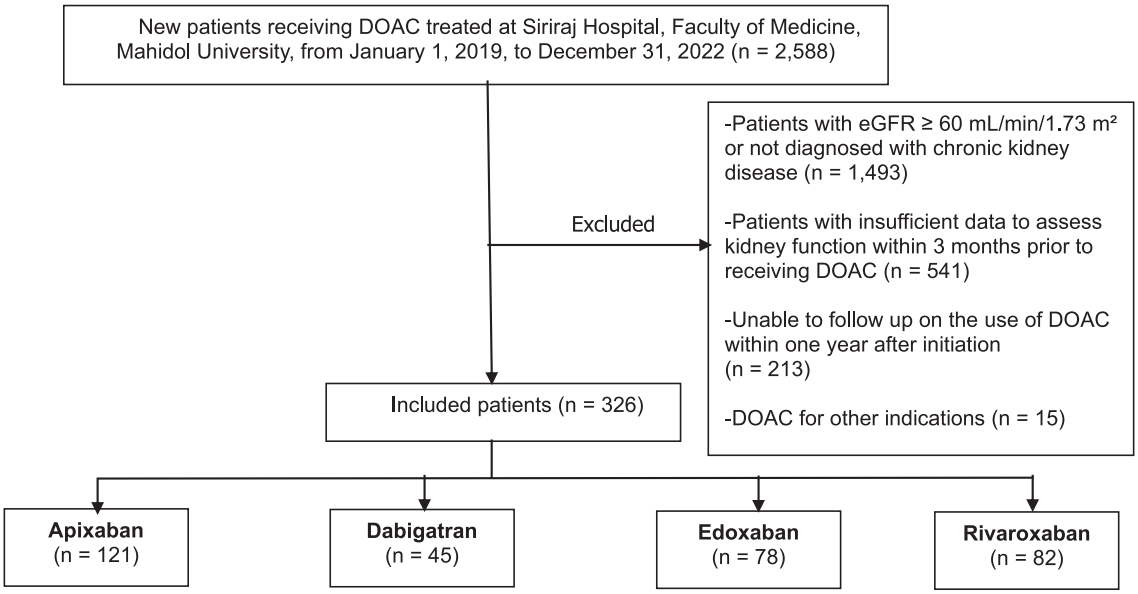

FIGURE 1 | Flow chart of the study. DOAC = direct oral anticoagulant, eGFR = estimated glomerular filtration rate.

of 45.6 ± 9.9 mL/min/1.73 m^2. Most patients had hypertension and dyslipidemia as their underlying diseases. Approximately 50% of patients had used warfarin before DOAC prescribing, and 38% of patients received aspirin concomitantly with the first DOAC use (Table 1).

3.1 | The Prescription of DOACs Complied With TFDA Recommendation

Of 1587 DOAC prescriptions during the study period, the percentage of DOAC dosing according to TFDA was 1083 prescriptions (68.2% of DOAC prescriptions). For prescriptions not adhering to the recommendations, over-dosing accounted for 15.8% and under-dosing accounted for 15.9%. When analyzing DOAC dosing patterns individually, patients receiving rivaroxaban and dabigatran had the highest adherence to recommended dosing (79.1% and 77.9%, respectively), followed by apixaban (63.3%) and edoxaban (57.0%).

For prescriptions not complying with the prescribing information, most patients receiving dabigatran (18.5%), edoxaban (35.2%), and rivaroxaban (10.7%) were overdosed. In contrast, most patients receiving apixaban who did not comply with the prescribing information were underdosed (28.4%) (Figure 2).

3.2 | Analysis of Renal Function From Various Equations

When eGFR was categorized by KDIGO classification (CKD-EPI equation), kidney function calculated from eGFR was significantly different from eCrCl. For the category of G1–G2 CKD, kidney function from eGFR (both CKD-EPI and CKD-EPI non-indexed for BSA) was significantly lower than that from eCrCl. In contrast, in the lower stages of KDIGO classification, specifically less than G3a, kidney function values from eGFR (both CKD-EPI and CKD-EPI non-indexed for BSA) were significantly higher than those from eCrCl (Table 2).

3.3 | Percentage of Agreement, Over-Dosing, and Under-Dosing When Compared eGFR to Standard eCrCl

The agreement between eGFR (CKD-EPI and CKD-EPI non-indexed for BSA) and eCrCl based on dosing cutoff recommendations by TFDA guidelines is presented in Table 3. The CKD-EPI and eCrCl were in agreement for 57.0% of DOAC prescriptions. Dosing according to CKD-EPI, which was higher than that of eCrCl (over-dosing category), was 39.5%. Dosing according to CKD-EPI, which was lower than eCrCl (under-dosing category), was 0.4%. The results for agreement, over-dosing, and under-dosing categories with CKD-EPI non-indexed for BSA were nearly identical to those from the CKD-EPI equation.

In addition, we explored sensitivity analyses to identify the eGFR cutoff values that lead to differences in dosing categories between the eGFR and eCrCl equations. The results showed that an eGFR (CKD-EPI) value of less than 45 mL/min/1.73 m^2 was associated with differences in the dosage category for DOAC dosing ($p < 0.001$, Pearson's Chi-Square test).

3.4 | Subgroup Analysis of Patients Receiving Apixaban With "Under-Dosing" According to TFDA

For apixaban dosing according to TFDA guidelines, patients who meet 2 out of 3 criteria (body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL, and age > 80 years) are considered eligible for low-dose apixaban (2.5 mg twice daily). We found that patients who were inappropriately prescribed low-dose apixaban did not meet the complete criteria for dose reduction. The majority of under-dosed patients (38.5%) met only the age criteria, while

TABLE 1 | Baseline characteristics.

Patient	Apixaban ($n = 121$, 37.1%)	Dabigatran ($n = 45$, 13.8%)	Edoxaban ($n = 78$, 23.9%)	Rivaroxaban ($n = 82$, 25.2%)	Total ($n = 326$, 100.0%)
Age (year) ± SD	80.4 ± 9.0	77.5 ± 11.0	80.8 ± 8.6	76.5 ± 8.2	79.1 ± 9.2
Male (%)	65 (51.6%)	27 (54.0%)	42 (52.5%)	52 (61.2%)	186 (54.5%)
Body weight (kg) ± SD	63.6 ± 14.4	67.3 ± 13.2	62.1 ± 12.3	69.2 ± 12.6	65.2 ± 13.6
Height (cm) ± SD	160.1 ± 8.8	161.4 ± 8.6	159.9 ± 9.5	162.7 ± 9.4	160.9 ± 9.1
BMI (kg/m^2) ± SD	24.8 ± 4.8	25.7 ± 3.9	24.2 ± 3.6	26.0 ± 3.7	24.9 ± 4.0
BSA (m^2) ± SD	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	1.8 ± 0.2	1.7 ± 0.2
Baseline kidney function					
Scr (mg/dL) ± SD	1.5 ± 0.6	1.3 ± 0.2	1.4 ± 0.3	1.3 ± 0.3	1.4 ± 0.4
eCrCl (mL/min) ± SD	33.1 ± 11.3	39.6 ± 12.2	34.6 ± 10.0	40.8 ± 10.5	36.4 ± 11.4
eGFR ($mL/min/1.73\,m^2$) ± SD	43.1 ± 10.8	48.9 ± 9.0	44.8 ± 9.8	47.7 ± 10.5	45.6 ± 9.9
eGFR non-indexed for BSA (mL/min) ± SD	43.4 ± 12.0	50.4 ± 11.2	44.9 ± 10.8	46.9 ± 9.9	45.6 ± 11.3
Complete blood count					
Hemoglobin (g/dL) ± SD	12.2 ± 2.0	12.5 ± 1.6	12.3 ± 2.0	12.8 ± 1.8	12.4 ± 1.9
Platelet (10^9/L) ± SD	215.4 ± 75.3	222.0 ± 68.8	214.9 ± 72.3	12.8 ± 1.8	215.7 ± 71.4
Underlying disease					
Hypertension (%)	108 (89.3%)	43 (95.6%)	63 (80.8%)	72 (87.8%)	286 (87.7%)
Dyslipidemia (%)	83 (68.6%)	30 (66.7%)	50 (64.1%)	59 (72.0%)	222 (68.1%)
Anemia (%)	71 (58.7%)	23 (55.1%)	39 (50.0%)	32 (39.0%)	165 (50.6%)
Diabetes mellitus (%)	58 (47.9%)	16 (35.6%)	29 (37.2%)	47 (57.3%)	150 (46.0%)
Coronary artery disease (%)	40 (33.1%)	15 (33.3%)	31 (39.7%)	43 (52.4%)	129 (39.6%)
Heart failure (%)	29 (24.0%)	9 (20.0%)	22 (28.2%)	24 (29.3%)	84 (25.8%)
Cancer (%)	20 (16.5%)	3 (6.7%)	11 (14.1%)	11 (13.4%)	45 (13.8%)
Hepatic disease (%)	7 (5.8%)	3 (6.7%)	5 (6.4%)	10 (12.2%)	25 (7.7%)
History of disease					
Prior stroke (%)	34 (28.1%)	15 (33.3%)	19 (24.4%)	14 (17.1%)	82 (25.2%)
Prior bleeding (%)	3 (2.5%)	2 (4.4%)	11 (14.1%)	5 (6.1%)	21 (6.4%)
Concomitant drug therapy					
Aspirin (%)	40 (33.1%)	19 (42.2%)	31 (39.7%)	35 (42.7%)	125 (38.3%)
P2Y12 inhibitors (%)	19 (15.7%)	11 (24.4%)	8 (10.3%)	18 (22.0%)	56 (17.2%)
Chronic steroid use (> 3 months) (%)	4 (3.3%)	1 (2.2%)	3 (3.8%)	3 (3.7%)	11 (3.4%)
Drugs for gastrointestinal ulcer prevention (%)	41 (33.9%)	18 (40.0%)	30 (38.5%)	21 (25.6%)	110 (33.7%)

Abbreviations: BMI = body mass index, BSA = body surface area, eCrCl = estimated creatinine clearance (Cockcroft-Gault equation), eGFR = estimated glomerular filtration rate, Scr = serum creatinine.

16.0% and 12.8% of patients met only the serum creatinine and body weight criteria, respectively. Notably, 23.5% of patients receiving apixaban did not meet any of the three criteria for low-dose apixaban consideration (Figure 3).

3.5 | Clinical Outcomes After One-Year Follow-Up

All patients in the study having non-valvular AF were prescribed DOACs for stroke prevention. Eight cases of stroke (2.5%

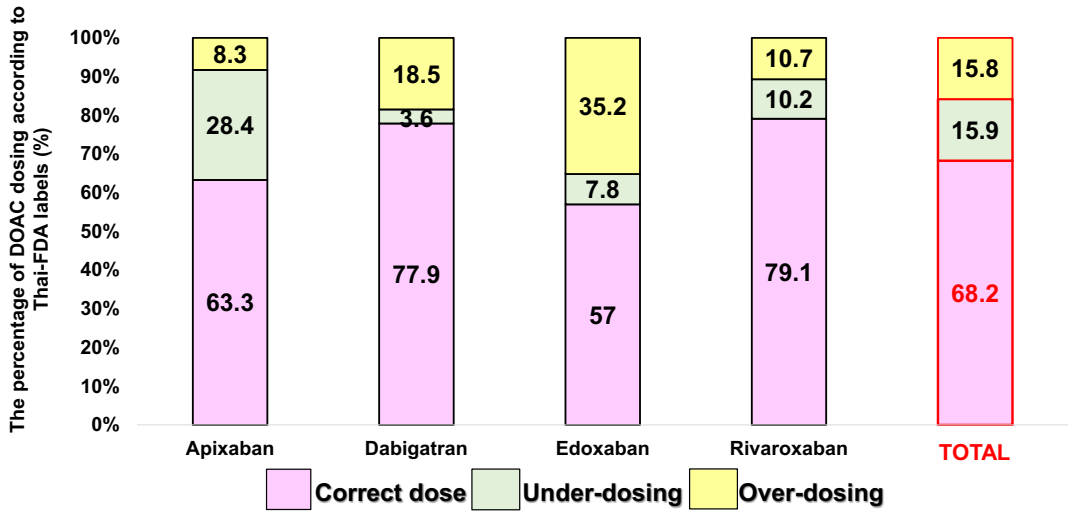

FIGURE 2 | The appropriateness of DOAC dosing according to Thai-FDA labels.

TABLE 2 | Mean difference between eGFR (CKD-EPI and CKD-EPI non-indexed for BSA) and eCrCl.

KDIGO classification (mL/min/1.73 m²)	eCrCl	eGFR (CKD-EPI)	eCrCl vs. CKD-EPI		eGFR (CKD-EPI non-indexed for BSA)	eCrCl vs. CKD-EPI non-indexed for BSA	
			Mean difference	*p*		Mean difference	*p*
G1-G2 (>60) *N* = 59	69.0 ± 10.8	60.2 ± 11.0	8.8 ± 11.2	< 0.001	59.2 ± 14.6	9.8 ± 12.7	< 0.001
G3a (45–59) *N* = 241	50.3 ± 3.8	54.6 ± 7.3	−4.3 ± 7.0	< 0.001	53.7 ± 9.3	−3.5 ± 8.9	< 0.001
G3b (30–44) *N* = 755	37.1 ± 4.2	47.0 ± 7.8	−9.9 ± 7.9	< 0.001	47.4 ± 10.6	−10.3 ± 11.1	< 0.001
G4 (15–29) *N* = 489	24.3 ± 3.8	36.5 ± 8.6	−12.2 ± 7.7	< 0.001	38.6 ± 11.5	−14.3 ± 10.9	< 0.001
G5 (<15) *N* = 43	12.1 ± 3.5	20.3 ± 8.2	−8.2 ± 5.7	< 0.001	24.1 ± 11.4	−12.0 ± 9.6	< 0.001

Abbreviations: BSA = body surface area, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eCrCl = estimated creatinine clearance, eGFR = estimated glomerular filtration rate, G = GFR category, KDIGO = Kidney Disease: Improving Global Outcomes.

of patients) were observed within 1 year after initiating DOAC therapy, across all DOAC types. Five patients experienced episodes of over-dosing more frequently than correct dosing or under-dosing, whereas three cases were exposed to on-label dosing more often than other dosing categories during our observation period.

Regarding safety outcomes from DOAC use, it was observed that out of a total of 326 patients using DOACs, 15 cases (4.6%) experienced bleeding events within 1 year of initiating DOAC therapy, across all DOAC types. When categorized by the type of bleeding, major bleeding events occurred in four cases (1.2%), which were associated with the use of apixaban, dabigatran, and edoxaban. Clinically relevant non-major bleeding events were noted in 11 cases (3.4%), across all DOAC types. There was no association between clinical outcome events (both stroke and bleeding) and the dosing categories of correct dosing, over-dosing, or under-dosing based on TFDA recommendation.

4 | Discussion

The study of DOAC dosing among various equations in patients with kidney impairment and the elderly found that the percentage of DOAC dosages correctly compliant with TFDA labels was approximately 70% of prescriptions during the 2019–2022 period. The proportion of over-dosing was around 16%, mainly found with dabigatran, edoxaban, and rivaroxaban. The dose discordance when using eGFR versus standard eCrCl was approximately 40%, with higher eGFR values from the CKD-EPI equation leading to over-dosing of DOAC usage.

Patients with impaired kidney function are likely to have inappropriate DOAC dosing. Leef GU et al. evaluated 5060 patients with newly diagnosed AF across various degrees of kidney function. They found that if patients' eGFR was less than 30 mL/min/1.73 m², the proportion of over-dosing of DOACs increased [19]. We intended to select patients with CKD to address practical dosing issues. A previous study of DOAC dosing from Thailand

TABLE 3 | Dosing agreement between eGFR (CKD-EPI and CKD-EPI non-indexed for BSA) and eCrCl equation.

CKD-EPI (mL/min/1.73 m²)		eCrCl (mL/min)			CKD-EPI vs. eCrCl equation
		< 30 mL/min/1.73 m²	30–50 mL/min/1.73 m²	> 50 mL/min/1.73 m²	Interpretation
< 30	Prescriptions[a] (%)	85 (7.8%)	0 (0.0%)	0 (0.0%)	% Agreement [total of 1083 prescriptions] 57.0%, 95% CI 53.99–59.97[b]
30–50	Prescriptions[a] (%)	42 (16.6%)	438 (40.4%)	1 (0.4%)	% Over-dosing [total of 251 prescriptions] 39.5%, 95% CI 33.43–45.82[b]
> 50	Prescriptions[a] (%)	0 (0.0%)	58 (22.9%)	95 (8.8%)	% Under-dosing [total of 253 prescriptions] 0.4%, 95% CI 0.01–2.20[b]

CKD-EPI non-indexed for BSA (mL/min)		eCrCl (mL/min)			CKD-EPI (non-indexed for BSA) vs. eCrCl equation
		< 30 mL/min/1.73 m²	30–50 mL/min/1.73 m²	> 50 mL/min/1.73 m²	Interpretation
< 30	Prescriptions[a] (%)	82 (7.6%)	0 (0.0%)	0 (0.0%)	% Agreement [total of 1083 prescriptions] 52.7%, 95% CI 49.68–55.71[b]
30–50	Prescriptions[a] (%)	36 (14.2%)	416 (38.4%)	1 (0.4%)	% Over-dosing [total of 253 prescriptions] 35.6%, 95% CI 29.70–41.84[b]
> 50	Prescriptions[a] (%)	4 (1.6%)	50 (19.8%)	73 (6.7%)	% Under-dosing [total of 251 prescriptions] 0.4% 95% CI 0.01–2.20[b]

[a]Number of prescriptions in each dosing category (green = agreement, yellow = over-dosing, pink = under-dosing).
[b]McNemar-Bowker Test.

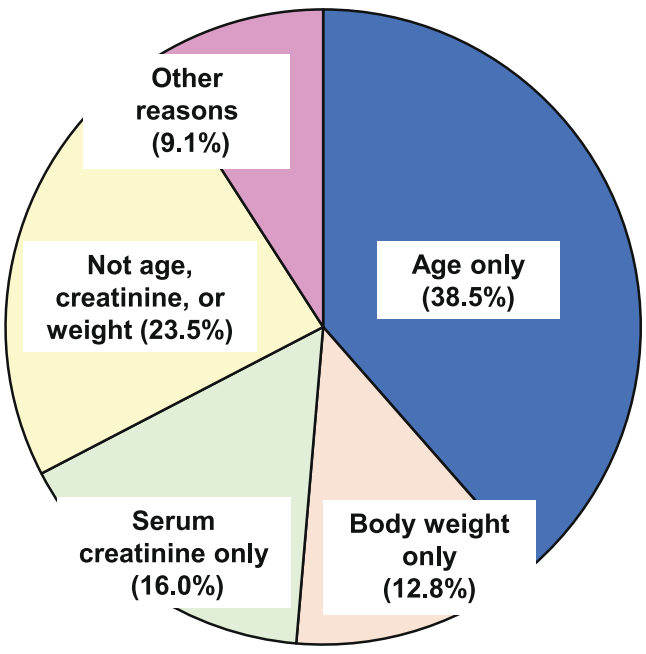

FIGURE 3 | The reasons for "Under-dosing" of apixaban prescription.

found that 70% of patients receiving their first DOAC had correct dosing [10], similar to our study; however, we examined all DOAC prescriptions during the study period, rather than just the first prescription. As CKD patients have gradually declining kidney function or have potential factors constantly affecting renal estimations, we considered that the information from all DOAC prescriptions during our two-year cross-sectional study (a total of 1587 DOAC prescriptions) would provide a more comprehensive picture of DOAC prescribing in real practice.

Several studies of DOACs in the majority of AF patients showed the prevalence of dosing according to eCrCl in the range of 43%–82% [13, 20, 21]. Our findings were quite similar to the ORBIT-AF II trial, an observational study in 1134 patients with AF and moderate CKD. They found that 66% of patients were appropriately dosed according to the prescribed eCrCl, whereas the proportion of under-dosing and over-dosing was nearly equal (15% and 20%, respectively) [21]. In terms of dose differences among renal equations, several studies explored the assumption that using other equations instead of eCrCl would result in dose discordance in the range of 25%–35% [22–24]. We found a statistically significant difference in eGFR and eCrCl

in every range of CKD staging. However, eGFR values in the range of 30–45 mL/min/1.73 m^2 provided 10 mL/min higher than eCrCl, which leads to different dosing suggestions. Our results were similar to a previous study that found the CKD-EPI equation significantly overestimated creatinine clearance (measured CrCl and eCrCl) in elderly individuals (10.3 ± 6.9 mL/min, $p < 0.001$) [25]. Rohla M et al. (2021), who studied DOAC dosing in AF patients with CKD, also found that the mean difference (SD) between eCrCl and eGFR (CKD-EPI) was significantly different, with higher values for CKD-EPI in patients with eCrCl less than the range of 30–44 mL/min [24]. Therefore, dosing suggestions may differ when using alternative renal equations besides eCrCl in kidney patients, especially those who have a low degree of kidney function.

When exploring the real situation of replacing eCrCl with eGFR (CKD-EPI) for dosing purposes, we tested the agreement and disagreement of DOAC dosing between these equations. The study found that 57% of prescriptions still recommended the same dosing regardless of whether eCrCl or CKD-EPI was used. However, the rest of the prescriptions showed dissimilar dosing suggestions, with a trend toward a higher dose when using CKD-EPI (40%). This finding has raised awareness that patients may be at risk of DOAC overdose when using equations other than the standard eCrCl recommendation. Taking into consideration previous findings that low levels of kidney function affect estimated kidney function, we conducted a sensitivity analysis and found that an eGFR cutoff of less than 45 mL/min/1.73 m^2 leads to different DOAC dosing in our study. This key finding can be applied in practice when eGFR (CKD-EPI) is automatically reported. When patients' eGFR is < 45 mL/min/1.73 m^2, these patients should be reevaluated using eCrCl equations for DOAC dosing purposes. However, this study was based on DOAC prescribing practices specific to our setting, and additional studies are required to evaluate the applicability of the eGFR cutoff differences across diverse clinical settings.

The eGFR from CKD-EPI non-indexed for BSA provides individual kidney function by taking patient weight into consideration. Glomerular filtration rate (GFR) is the best overall index of kidney function, which varies according to age, sex, and body weight [2]. Drug clearance is more strongly associated with non-index GFR (mL/min) than indexed GFR (mL/min/1.73 m^2). The latest KDIGO 2024 guidelines recommend that in people with extremes of body weight, eGFR non-indexed for BSA may be indicated [2]. A recent study of kidney transplant patients with obesity and a mean eGFR of 59 mL/min found that non-indexed GFR values accounting for actual BSA should be used for medication dosing [26]. Our included patients had a normal weight (mean BSA of 1.70 m^2), corresponding to the general Asian population. Not surprisingly, the results of the dosage agreement pattern between eCrCl versus CKD-EPI non-indexed for BSA were quite similar to those versus CKD-EPI equation. However, if a drug is used in patients with extremes of body weight, eGFR based on actual BSA should be performed to adjust dosing appropriately.

Clinical perspectives for DOAC dosing in elderly patients with CKD not only consider kidney function but also regard other attributes associated with changing patient factors. The study found that the number of underdosing prescriptions for apixaban (28%) was much higher than that of overdosing (8%). A lower dose of apixaban (2.5 mg twice daily) is needed in patients who have at least two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine ≥ 1.5 mg/dL. The most common reason for underdosing we found was that patients had incomplete criteria for dose reduction (e.g., patients who only met the age criteria of ≥ 80 years and received low-dose apixaban). An unintentional dose reduction may pose a thromboembolic risk to patients. In addition to apixaban, dabigatran and edoxaban also have recommended dosage adjustments that consider the patient's age, body weight, in addition to renal function [14–16]. In clinical practice, pharmacists have an important role in determining optimal DOAC dosing and detecting drug-related problems. In patients who have acute illnesses, unstable conditions related to an increased risk of bleeding, or are receiving drugs that can interact with DOACs, a reduced DOAC dosage may be considered. Considering this fact, additional monitoring in some situations, in addition to guideline dosing, also supports the safe and efficient use of DOACs.

For clinical outcomes after a one-year follow-up period, we found a low incidence of stroke (2.5%) and a low incidence of bleeding events (4.6%). Given the low number of adverse events, we could not find an association of clinical complications with the under-dosing or over-dosing groups of patients. As we collected clinical information through patient chart reviews, the incidence of bleeding may be under-reported, especially if patients experienced non-major bleeding. However, our results provided similar findings to a previous real-world study of DOACs in the Thai population, which found the incidence of bleeding in the range of 5.1%–13.0% [10]. More data are needed for further application regarding the clinical impact of DOAC dosing among various renal equations for non-valvular AF patients.

We acknowledge the limitations of the retrospective analysis based on the hospital database, which prevented us from exploring complete epidemiological data or determining the actual reasons for the observed DOAC dosing. To address this, we thoroughly reviewed hospitalization records to identify relevant clinical endpoints, including systemic thromboembolic events and hemorrhagic complications, in both outpatient and inpatient settings to account for any changes in dosing during the study period. The dosing definitions were based on TFDA recommendations, which consider renal function along with patient-specific factors to account for interindividual variability and clinical significance. However, the sample size calculation in our study was not adequately powered to detect differences in clinical outcomes; therefore, interpretation should be cautious. The data were obtained from tertiary-care university hospitals, which limit generalizability to such settings. Nonetheless, our study can represent hospitals with a high volume of DOAC prescriptions, revealing prescribing patterns that can be implemented in real-world drug usage. The obtained data will be considered alongside clinical outcomes to guide appropriate DOAC use in our university teaching hospital. This hospital frequently receives referrals from across the country, encountering a significant number of complex cases. As a result, it can represent DOAC usage for Thai patients or in similar contexts.

5 | Conclusion

DOAC prescribing complied with Thai FDA-approved labels in 70% of elderly patients with kidney impairment. The proportions of over-dosing and under-dosing were similar. When substituting eGFR (CKD-EPI) for eCrCl, we observed a dose disagreement of 45%, with trends toward a higher dose when using CKD-EPI equations. A patient's eGFR by CKD-EPI value of less than 45 mL/min/1.73 m^2 may pose a risk of dose discordance that should be recalculated to the standard eCrCl in our setting. The incidence of stroke and bleeding was low and nearly similar across all DOACs during the one-year follow-up period. Our study, conducted in a resource-limited country, still supports renal equations according to product-approved dosing, especially in patients with moderate to severe kidney impairment.

Author Contributions

S.S. wrote the manuscript, designed the research, performed the research, and analyzed the data; S.C. designed the research, performed the research, and wrote the manuscript; P.T., R.S., A.L., and N.K. performed the research and analyzed the data; R.C. designed the research; J.K. designed the research, performed the research, analyzed the data, wrote the manuscript, and provided supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.