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ORIGINAL INVESTIGATIONS

Non–Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction

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ABSTRACT

BACKGROUND Dose reduction of non–vitamin K antagonist oral anticoagulants (NOACs) is indicated in patients with atrial fibrillation (AF) with renal impairment. Failure to reduce the dose in patients with severe kidney disease may increase bleeding risk, whereas dose reductions without a firm indication may decrease the effectiveness of stroke prevention.

OBJECTIVES The goal of this study was to investigate NOAC dosing patterns and associated outcomes, i.e., stroke (ischemic stroke and systemic embolism) and major bleeding in patients treated in routine clinical practice.

METHODS Using a large U.S. administrative database, 14,865 patients with AF were identified who initiated apixaban, dabigatran, or rivaroxaban between October 1, 2010, and September 30, 2015. We examined use of a standard dose in patients with a renal indication for dose reduction (potential overdosing) and use of a reduced dose when the renal indication is not present (potential underdosing). Cox proportional hazards regression was performed in propensity score–matched cohorts to investigate the outcomes.

RESULTS Among the 1,473 patients with a renal indication for dose reduction, 43.0% were potentially overdosed, which was associated with a higher risk of major bleeding (hazard ratio: 2.19; 95% confidence interval: 1.07 to 4.46) but no statistically significant difference in stroke (3 NOACs pooled). Among the 13,392 patients with no renal indication for dose reduction, 13.3% were potentially underdosed. This underdosing was associated with a higher risk of stroke (hazard ratio: 4.87; 95% confidence interval: 1.30 to 18.26) but no statistically significant difference in major bleeding in apixaban-treated patients. There were no statistically significant relationships in dabigatran- or rivaroxaban-treated patients without a renal indication.

CONCLUSIONS In routine clinical practice, prescribed NOAC doses are often inconsistent with drug labeling. These prescribing patterns may be associated with worse safety with no benefit in effectiveness in patients with severe kidney disease and worse effectiveness with no benefit in safety in apixaban-treated patients with normal or mildly impaired renal function. (J Am Coll Cardiol 2017;69:2779–90) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

CrCl = creatinine clearance

eGFR = estimated glomerular filtration rate

FDA = U.S. Food and Drug Administration

HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, and drugs or alcohol

HR = hazard ratio

IQR = interquartile range

NOAC = non-vitamin K antagonist oral anticoagulant

SCr = serum creatinine

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a 5-fold increased risk of stroke (1). The introduction of non-vitamin K antagonist oral anticoagulants (NOACs) has been a major advance in stroke prevention in patients with AF. Compared with warfarin, NOACs are more convenient to use and demonstrate at least equivalent efficacy, with less intracranial bleeding, in pivotal clinical trials (2–5). All NOACs have some degree of renal clearance (80% for dabigatran, 50% for edoxaban, 35% for rivaroxaban, and 27% for apixaban), and dose reduction is indicated in patients with clinically significant renal impairment (6,7). Failure to reduce the dose in patients with severe renal disease may increase the risk of bleeding, whereas inappropriate dose reduction without a firm indication may decrease the effectiveness of stroke prevention.

Recent registry data suggest that inappropriate NOAC dosing is not uncommon. In ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), more than one-half of the dabigatran-treated patients with creatinine clearance (CrCl) ≤30 ml/min received the standard dose, whereas 11% of patients with CrCl >30 ml/min received the reduced dose (8). In XANTUS (Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation), a Phase IV observational study of patients with AF prescribed rivaroxaban, more than one-third of patients with CrCl <50 ml/min received the standard dose, whereas 15% of patients with CrCl ≥50 ml/min received the reduced dose (9). Although these registries provide some important insights, they are still selective (e.g., patients enrolled were mostly treated by specialists) (10); thus, they may have underestimated the extent of inappropriate dosing in everyday clinical practice. Furthermore, few data exist on how potential underdosing or overdosing affects the effectiveness or safety of these drugs.

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Therefore, the goal of the present study was to investigate patterns of NOAC dosing and the associated risks of stroke and major bleeding in a large heterogeneous cohort of patients with AF initiating NOACs in routine clinical practice. Specifically, we examined the use and outcomes of a standard dose in patients with a renal indication for dose reduction (potential overdosing), as well as the use and outcomes of a reduced dose in patients with no renal indication for dose reduction (potential underdosing). We hypothesized that overdosing may be related to worse safety (a higher risk of major bleeding) and underdosing may be related to worse effectiveness (a higher risk of ischemic stroke or systemic embolism).

METHODS

This retrospective analysis was conducted by using administrative claims and linked laboratory data from OptumLabs Data Warehouse, which contains >100 million privately insured and Medicare Advantage enrollees over the last 20 years throughout the United States (11,12). Approximately one-third of the patients with claims data had linked serum creatinine (SCr) laboratory results.

A total of 14,865 patients with nonvalvular AF were identified who initiated apixaban, dabigatran, or rivaroxaban between October 1, 2010, and September 30, 2015, and had creatinine test results before treatment initiation. Patients with valvular heart disease, an estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2 (7), or with other indications for NOACs (e.g., prophylaxis and treatment of venous thromboembolism) were excluded. Further cohort definition details can be found in the Online Appendix and Online Figure 1.

The present study was exempt by the Mayo Clinic Institutional Review Board for approval because only pre-existing, de-identified data were used.

RENAL FUNCTION AND INDICATION FOR DOSE REDUCTION. The most recent SCr levels within 1 year before treatment initiation were abstracted. We calculated eGFR by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (13). Patients were considered to have a renal indication for dose reduction if they were prescribed dabigatran and had an eGFR <30 ml/min/1.73 m^2, rivaroxaban and an eGFR <50 ml/min/1.73 m^2, or apixaban and an SCr level ≥1.5 mg/dl. The indication for dose reduction with apixaban (per the approved product label) is more complex than our criteria and requires 2 of the following 3 criteria: age ≥80 years, weight ≤60 kg, and SCr level ≥1.5 mg/dl. Because weight is not available in our database, our main analyses relied on SCr level as the apixaban dose indication. Numerous sensitivity tests were conducted to vary the definition of indication for dose reduction; these tests are described later along with all other sensitivity analyses.

We considered drug interactions with P-glycoprotein and cytochrome P450 3A4 inhibitors based on European Heart Rhythm Association guidelines (6). We did not include use of these medications in the criteria for dose reduction because they are generally considered

relative indications, and the effects on NOAC plasma levels vary substantially among patients and drugs. The most commonly used interacting medications in this cohort were diltiazem, amiodarone, dronedarone, and verapamil; we included use of these medications as matching variables in propensity score models and conducted subgroup analyses according to drug interactions.

Further details on NOAC dosage, drug interactions, and the assessment of renal function are given in the Online Appendix.

STUDY ENDPOINTS. The primary effectiveness outcome was ischemic stroke or systemic embolism, and the primary safety outcome was major bleeding. We included outcomes that occurred on treatment and censored patients at the earliest date of the end of enrollment in health plans, the end of the study period (September 30, 2015), discontinuation of treatment, or switching to another oral anticoagulant agent. Further details are provided in the Online Appendix and Online Table 1.

STATISTICAL ANALYSIS. Percentages of patients with a renal indication for dose reduction but who received standard dose NOACs (potential overdosing) were assessed. Also assessed were the percentages of patients with no renal indication but receiving reduced dose NOACs (potential underdosing).

Propensity score matching was used to balance the differences in baseline characteristics between patients receiving a reduced dose versus a standard dose. A propensity score (the probability of receiving a reduced dose) was estimated by using logistic regression based on 50 baseline characteristics, including sociodemographic characteristics, comorbidities, and concomitant medication use. Nearest neighborhood caliper matching was used to match patients based on the logit of the propensity score using a caliper equal to 0.2 of the SD of the logit of the propensity score (14). In patients with a renal indication for dose reduction, 1:1 matching without replacement was used because the numbers of patients receiving a standard or reduced dose were similar. In patients without a renal indication for dose reduction, 1:5 propensity score matching with replacement was used because there were more patients who received a standard dose than a reduced dose.

Among apixaban-treated patients (the group with the smallest percentage of patients receiving a standard dose), the ratio of patients receiving a standard dose versus a reduced dose was approximately 5. A weight was calculated and used in the analyses to account for the larger size of the standard dose groups and the possibility some patients in the standard dose groups were used as control subjects multiple times (15). Therefore, in the tables and figures of the Results, the number of patients receiving a standard dose was the weighted number of patients, equal to the number of patients receiving a reduced dose. Standardized difference was used to assess the balance of covariates after matching, and a standardized difference <10% was considered acceptable (16). If a covariate was not balanced, we examined whether including it in the regression affected results.

Cox proportional hazards regression was used to compare stroke and bleeding outcomes in each propensity score–matched cohort, with robust sandwich estimates to account for the clustering within matched sets (17). NOAC dose was the only exposure variable included in the regression. In the analysis of patients with a renal indication for dose reduction, because of the small number of patients, we pooled the 3 NOACs for the main analysis to increase power, but patients were exact-matched on the NOACs. In the analysis of patients without a renal indication for dose reduction, each drug was examined separately. The proportional hazard assumption was tested on the basis of Schoenfeld residuals (18) and was valid for all outcomes.

SENSITIVITY ANALYSIS. A number of sensitivity analyses were conducted, as summarized in Online Table 2. First, in patients with an indication for dose reduction, we required apixaban-treated patients to be ≥80 years of age and to have an SCr level ≥1.5 mg/dl; thus, all patients in this analysis have a firm indication for dose reduction.

Second, when analyzing patients with no renal indication, an eGFR ≥50 ml/min/1.73 m^2 was required for all 3 drugs. The reasons are 2-fold. First, nearly one-half of the dabigatran-treated patients with no renal indication for dose reduction but who were taking a reduced dose had an eGFR between 30 and 50 ml/min/1.73 m^2. Those patients would qualify for dose reduction with dabigatran 110 mg in Europe, but this dose was not approved by the U.S. Food and Drug Administration (FDA). Second, the apixaban label considers age, weight, and creatinine level in dosing guidelines, but these factors are also considered in the eGFR calculation. Moreover, apixaban's renal indication for dose reduction (SCr level ≥1.5 mg/dl) correlates closely with eGFR <50 ml/min/1.73 m^2, which is the renal indication for rivaroxaban, a similar direct factor Xa inhibitor with a comparable percentage of renal excretion. Therefore, in this sensitivity analysis, eGFR ≥50 ml/min/1.73 m^2 was defined as a lack of indication for dose reduction for all 3 NOACs.

Third, we used inverse probability of treatment weighting instead of propensity score matching

TABLE 1 Baseline Patient Characteristics

	With Renal Indication (n = 1,473)	Without Renal Indication (n = 13,392)	Total (N = 14,865)
Age, yrs	77.5 ± 8.4	69.9 ± 10.9	70.6 ± 10.9
18–64	8.1	31.0	28.7
65–74	23.2	32.7	31.8
75–79	21.2	15.5	16.0
≥80	47.5	20.8	23.5
eGFR, ml/min/1.73 m^2	37.8 ± 8.4	73.4 ± 17.2	69.9 ± 19.7
<30	22.0	0.0	2.2
30–50	77.5	7.8	14.7
50–80	0.5	55.0	49.6
>80	0.0	37.1	33.5
Female	49.5	41.8	42.6
Nonwhite race	22.1	23.3	23.1
Medical history			
Heart failure	51.7	28.3	30.7
Hypertension	97.8	89.0	89.9
Diabetes mellitus	54.2	40.2	41.6
Thromboembolism*	20.2	13.8	14.4
Vascular disease	43.2	26.8	28.4
Hyperlipidemia	86.8	81.7	82.2
Cardioversion	10.0	12.9	12.6
Ablation	1.0	4.3	3.9
PCI	3.7	2.3	2.4
CABG	1.4	1.1	1.1
Pacemaker/ICD	20.9	13.6	14.3
Any bleeding	13.1	9.8	10.1
Intracranial bleeding	1.5	1.0	1.1
Anemia	47.5	24.5	26.8
Coagulation or platelet defect	12.1	7.9	8.3
Liver disease	4.3	4.9	4.8
Cancer	16.0	13.7	13.9
Depression	16.7	13.2	13.5
Hypothyroidism	29.1	24.9	25.3
Thyrotoxicosis	2.0	2.9	2.8
Dementia	10.1	5.1	5.6
COPD	14.6	10.0	10.4
Sleep apnea	15.5	18.5	18.2
Falls	10.4	5.6	6.0
Alcoholism	2.2	2.5	2.5
Obesity	18.1	20.3	20.1
Smoking	17.0	18.2	18.1
Medication use			
Antiplatelets	12.2	7.1	7.6
NSAIDs	4.3	4.8	4.8
Amiodarone	13.2	8.7	9.2
Dronedarone	2.6	4.0	3.9
Other antiarrhythmic drugs	6.2	11.8	11.3
Digoxin	9.4	11.5	11.3
Diltiazem	14.9	16.5	16.3
Verapamil	1.2	1.7	1.7
Adrenergic blockers	65.9	59.0	59.7
Renin angiotensin system antagonists	48.3	47.7	47.8
Diuretics	48.9	28.8	30.8
Metformin	8.0	12.5	12.0
Insulin	16.3	7.8	8.6
Proton pump inhibitors	23.3	18.4	18.9
Histamine$_2$-antagonists	3.7	2.3	2.4

Continued on the next page

to repeat the main analyses; that is, using a weight of 1/propensity score for patients receiving a reduced dose and 1/(1 − propensity score) for patients receiving a standard dose (19).

Fourth, because factors such as age, sex, drug interactions, and baseline risk of bleeding measured by using the HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, and drugs or alcohol) score may also affect the decision to reduce dose, we conducted subgroup analyses on the basis of these factors.

Fifth, in the main analyses of patients with a renal indication for dose reduction, we pooled 3 NOACs because of the small sample size. Additional analyses were performed by examining the outcomes associated with using standard doses versus reduced doses for each medication separately.

Sixth, intracranial bleeding was examined in each propensity score–matched cohort, which was not included in the main analyses due to the small number of events.

Lastly, we repeated the analyses by using 3 pre-specified falsification endpoints; these endpoints were inpatient admission due to sepsis, pneumonia, and chronic obstructive pulmonary disease, which are outcomes unlikely to occur as a result of NOAC dose reduction. This method can provide some insights on whether there is residual confounding after propensity score matching (20).

Further details of the methods are provided in the Online Appendix. All analyses were conducted by using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina) and Stata version 14.1 (StataCorp, College Station, Texas).

RESULTS

A total of 1,473 patients had a renal indication for dose reduction. Among these patients, the median age was 79 years (interquartile range [IQR]: 73 to 84 years), the median GFR was 39 ml/min/1.73 m^2 (IQR: 31 to 45 ml/min/1.73 m^2), the median CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score was 5 (IQR: 4 to 6), and the median HAS-BLED score was 4 (IQR: 3 to 4) (Table 1). Patients were followed up for a median of 3.6 months (IQR: 1.5 to 8.4 months).

In the 13,392 patients without a renal indication for dose reduction, the median age was 70 years (IQR: 63 to 78 years), the median eGFR was 73 ml/min/1.73 m^2 (IQR: 60 to 86 ml/min/1.73 m^2), the median CHA_2DS_2-VASc was 4 (IQR: 2 to 5), and the median HAS-BLED

score was 2 (IQR: 2 to 3) (**Table 1**). Patients were followed up for a median of 4.0 months (IQR: 1.0 to 9.6 months).

The detailed follow-up data according to drug and indication for dose reduction, as well as patient characteristics before and after propensity score matching, are presented in Online Tables 3 to 7.

Among patients with a renal indication for dose reduction, 43.0% received standard doses (**Figure 1**). Among patients with no renal indication for dose reduction, 13.3% received reduced doses (**Figure 2**). Additional data regarding NOAC dosing patterns in subgroups (e.g., sex, eGFR categories, drug interactions, obesity, prescriber specialty) are presented in Online Tables 8 and 9. The results from multivariable logistic regression of predictors of NOAC dose reduction are presented in Online Tables 10 and 11.

Among patients with a renal indication for dose reduction, the stroke event rate was 2.32 and 1.85 per 100 person-years in the standard dose and reduced dose NOACs, respectively; the event rate for major bleeding was 11.29 and 5.06 per 100 person-years in the standard dose and reduced dose NOACs (**Table 2**). There was no statistically significant difference in the risk of stroke comparing a standard dose versus a reduced dose (hazard ratio [HR]: 1.66; 95% confidence interval [CI]: 0.40 to 6.88). However, bleeding risk was significantly higher in patients prescribed standard dose NOACs (HR: 2.19; 95% CI: 1.07 to 4.46) (**Figure 3**). When examining each drug separately, there was a signal of worse safety across all drugs, but the results of stroke were limited by the small number of events (Online Table 12).

Among patients with no renal indication for dose reduction, the event rate for stroke was 1.43 and 1.70 per 100 person-years in the standard dose and reduced dose NOACs, respectively; the event rate for major bleeding was 5.03 and 5.43 per 100 person-years in the standard and reduced dose NOACs (**Table 3**). Use of a reduced dose apixaban was associated with a nearly 5-fold higher risk of stroke (HR: 4.87; 95% CI: 1.30 to 18.26) but a similar risk of major bleeding (HR: 1.29; 95% CI: 0.48 to 3.42) compared with standard dose apixaban. There was no statistically significant relationship between dose reduction and risk of stroke or bleeding in the dabigatran- or rivaroxaban-treated patients (**Figure 4**).

Results from all sensitivity and subgroup analyses were generally consistent with the main analysis (Online Tables 12 to 25). For instance, when inverse probability of treatment weighting was used instead of propensity score matching, potential overdosing was associated with a higher risk of major bleeding (HR: 2.24; 95% CI: 1.18 to 4.24 for the 3 NOACs pooled), with a similar risk of stroke (Online Table 17). Potential underdosing of apixaban was associated with a nonsignificant trend toward higher risk of stroke but a similar risk of major bleeding; conversely, potential underdosing of rivaroxaban was associated with a nonsignificant trend toward lower risk of stroke (Online Table 18). Additional data, such as types of major bleeding and cumulative risks, can be found in Online Table 26 and Online Figures 2 to 6.

TABLE 1 Continued

	With Renal Indication (n = 1,473)	Without Renal Indication (n = 13,392)	Total (N = 14,865)
CHA_2DS_2-VASc			
0–1	0.5	12.4	11.2
2–3	15.8	37.0	34.9
≥4	83.8	50.6	53.9
HAS-BLED score ≥3	95.1	39.6	45.1
Prescribing provider specialty			
Cardiologist	48.6	53.0	52.5
Internal/family medicine	26.6	20.9	21.4
Other	24.8	26.2	26.0
Warfarin experienced	31.4	27.2	27.6

Values are mean ± SD or %. Pre- and post-matching baseline characteristics for patients with and without renal indication for dose reduction are given in Online Tables 9 to 12. *Arterial, including ischemic stroke, systemic embolism, and transient ischemic attack.

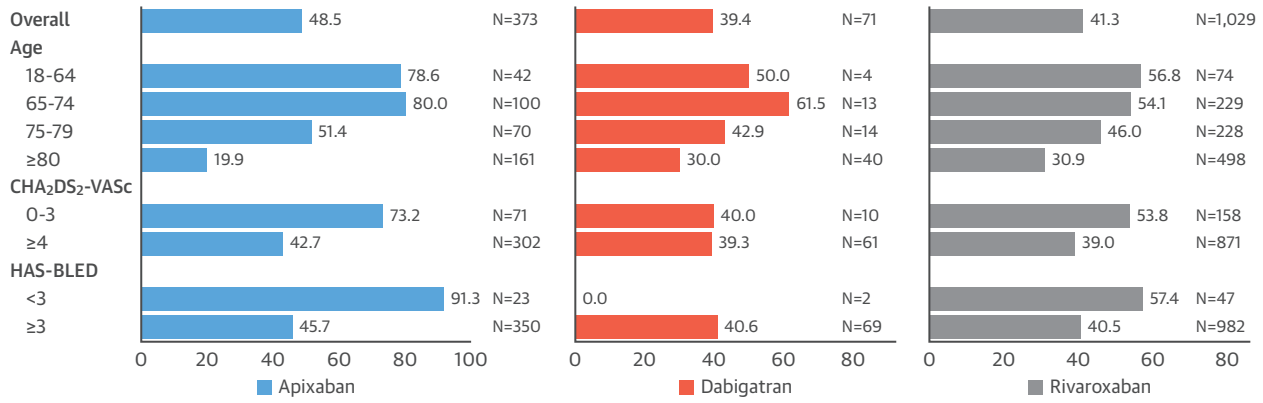
CABG = coronary artery bypass grafting; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 yrs, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, and drugs or alcohol; ICD = implantable cardioverter-defibrillator; NSAID = nonsteroidal anti-inflammatory drug; PCI = percutaneous coronary intervention.

DISCUSSION

In this large-scale analysis of NOAC dosing patterns and associated outcomes in routine clinical practice, the prescribed doses were often inconsistent with the renal dose specified by FDA labeling (**Central Illustration**). We leveraged this variation in practice patterns to assess the potential effects of overdosing and underdosing on clinical outcomes. The data suggest that use of standard dose NOACs in patients with severe renal impairment was associated with a higher risk of major bleeding without any decrease in stroke risk. Conversely, apixaban dose reduction in patients with no severe renal impairment was related to reduced effectiveness for stroke prevention without any safety benefit.

NOAC dosing is complex, and there are many factors beyond renal function that may drive a clinician's choice of an initial dose. Frontline clinicians often find themselves making difficult dosing decisions for complex patients; they must assess competing stroke and bleeding risks, anticipate dynamic changes in

FIGURE 1 Percentage of Patients Overdosed

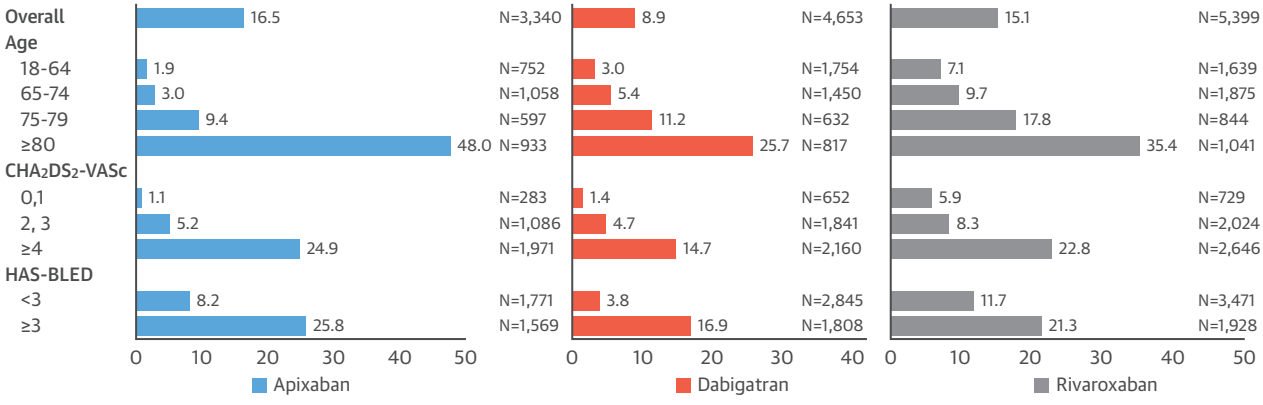


The percentage of patients who had a renal indication for dose reduction but received standard dose non-vitamin K antagonist oral anticoagulant was decreased in older, riskier patients. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, and drugs or alcohol.

renal function, account for the use of interacting medications, and assess patient frailty to determine an initial dose. These challenges are further compounded by the fact that the most complex cases, such as patients with severe kidney disease and previous intracranial bleeding, were either excluded or underrepresented in pivotal NOAC trials. Indeed, the observed stroke and bleeding rates were higher in our cohort than in pivotal clinical trials. Future large trials to explore outcomes of different doses are not feasible either, because patients cannot be deliberately underdosed or overdosed in a clinical trial. Thus, although our determination of an "appropriate" dose for a patient based on administrative data is imperfect, the findings provide valuable and unique insights to guide clinical decision-making.

It might be surprising that >40% of patients with a renal indication for dose reduction did not receive a reduced dose, but our results are consistent with previous U.S. and international studies (8,9). In patients with a renal indication for dose reduction,

FIGURE 2 Percentage of Patients Underdosed



The percentage of patients who did not have a renal indication for dose reduction but received reduced dose non-vitamin K antagonist oral anticoagulants was increased in older, riskier patients. Abbreviations as in Figure 1.

TABLE 2 Events and Event Rates in Patients With Renal Indication for Dose Reduction

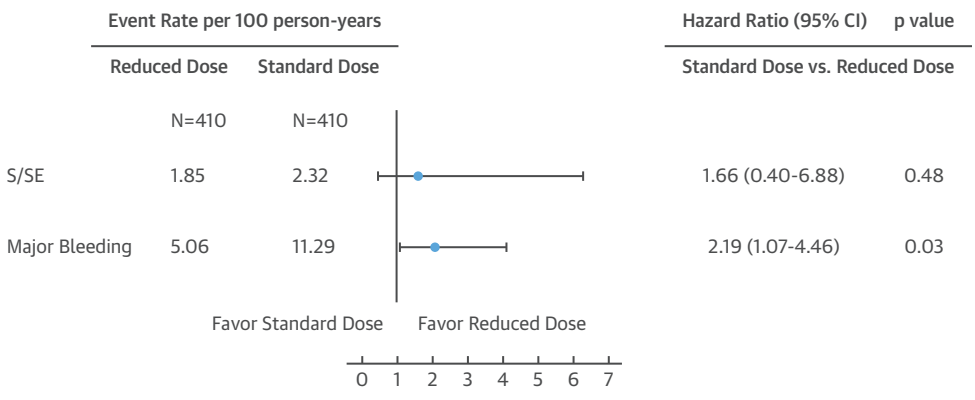
	Reduced Dose			Standard Dose		
	Event (n)	Total Follow-Up (PY)	Event Rate per 100 PY (95% CI)	Event (n)	Total Follow-Up (PY)	Event Rate per 100 PY (95% CI)
Overall		(N = 410)			(N = 410)	
S/SE	4	216.25	1.85 (0.70–6.54)	5	215.68	2.32 (0.97–6.91)
Major bleeding	11	217.30	5.06 (2.83–9.90)	24	212.53	11.29 (7.58–17.47)
Apixaban		(n = 77)			(n = 77)	
S/SE	2	28.23	7.08 (1.52–69.28)	0	28.40	0.00 (NA)
Major bleeding	1	28.61	3.49 (NA)	3	28.22	10.63 (3.32–50.71)
Dabigatran		(n = 19)			(n = 19)	
S/SE	0	18.51	0.00 (NA)	0	11.39	0.00 (NA)
Major bleeding	0	18.51	0.00 (NA)	2	11.33	17.65 (3.59–159.21)
Rivaroxaban		(n = 314)			(n = 314)	
S/SE	2	169.51	1.18 (0.26–11.45)	5	175.89	2.84 (1.19–8.47)
Major bleeding	10	170.17	5.88 (3.19–11.94)	19	172.98	10.98 (7.01–18.05)

CI = confidence interval; NA = not applicable; PY = person-years; S/SE = ischemic stroke/systemic embolism.

those receiving a standard dose, in general, had better renal function than those receiving a reduced dose (mean eGFR 39.9 ml/min/1.73 m^2 vs. 36.3 ml/min/1.73 m^2), but this difference was not substantial enough to explain the large proportion of patients who did not receive dose reduction. We also assessed variations of renal function at baseline and follow-up, but most of these patients did not have another eGFR result high enough to justify using the standard dose. It is possible that some patients were prescribed a standard dose but took only one-half of the pill in an attempt to extend their supply and reduce costs. However, all patients in our cohort had pharmacy insurance coverage; thus, most patients only paid a fraction of the overall medication cost, and the out-of-pocket costs for patients receiving standard or reduced doses were similar. Moreover, splitting pills is difficult for reducing the rivaroxaban dose from 20 mg to 15 mg.

Potential overdosing (i.e., use of standard dose NOACs in patients with severe renal impairment) was associated with a doubled risk of bleeding with no attendant reduction in the risk of stroke. One might expect that increased NOAC exposure would further reduce stroke risk, but this observation suggested that the stroke reduction effect plateaued with

FIGURE 3 Outcomes Associated With Overdosing



Among patients with a renal indication for dose reduction, event rates for ischemic stroke and systemic embolism (S/SE) and major bleeding and hazard ratios comparing a standard dose versus a reduced dose non–vitamin K antagonist oral anticoagulant (potential overdosing effect) favored the reduced dose. CI = confidence interval.

TABLE 3 Events and Event Rates in Patients Without Renal Indication for Dose Reduction

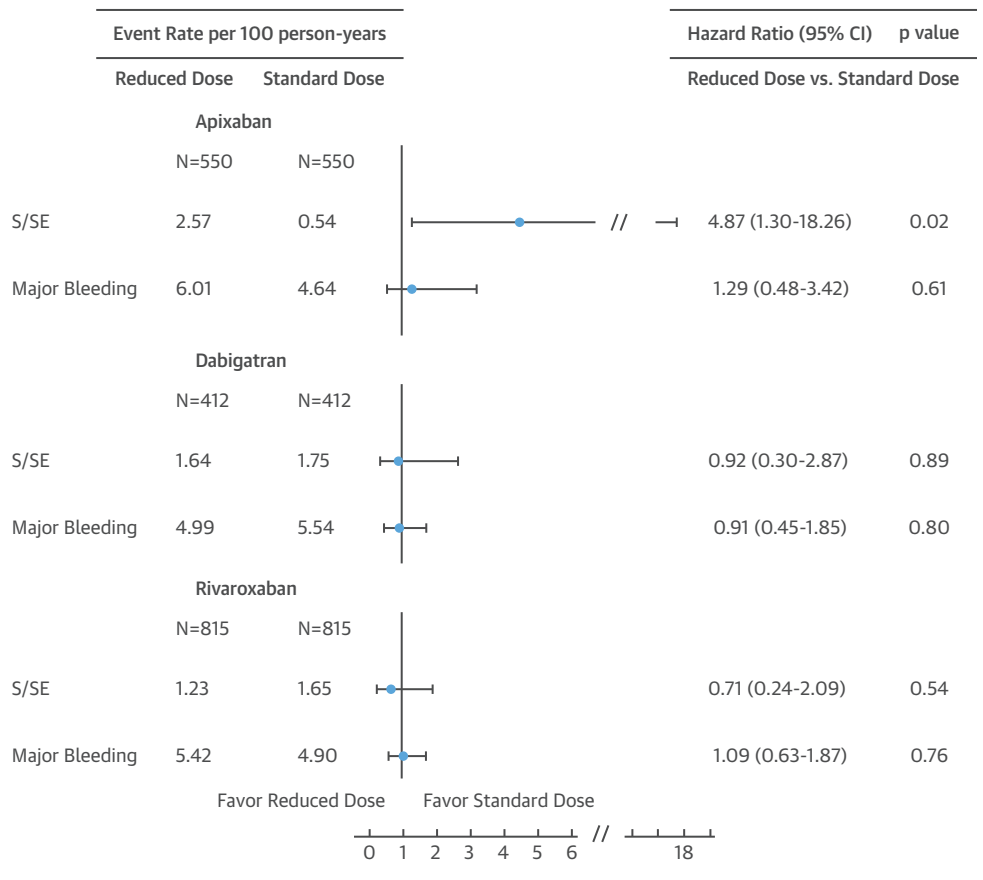
	Reduced Dose			Standard Dose		
	Event (n)	Total Follow-Up (PY)	Event Rate per 100 PY (95% CI)	Event (n)	Total Follow-Up (PY)	Event Rate per 100 PY (95% CI)
Overall	(N = 1,777)			(N = 1,777)		
S/SE	16	943.75	1.70 (1.05-2.91)	14	978.16	1.43 (0.93-2.33)
Major bleeding	51	939.02	5.43 (4.14-7.25)	49	974.03	5.03 (3.78-6.84)
Apixaban	(n = 550)			(n = 550)		
S/SE	6	233.33	2.57 (1.17-6.80)	1	220.59	0.54 (0.19-2.23)
Major bleeding	14	232.92	6.01 (3.61-10.74)	10	219.69	4.64 (1.92-13.96)
Dabigatran	(n = 412)			(n = 412)		
S/SE	5	304.40	1.64 (0.69-4.88)	5	285.75	1.75 (0.86-4.10)
Major bleeding	15	300.43	4.99 (3.03-8.76)	16	284.59	5.54 (3.35-9.84)
Rivaroxaban	(n = 815)			(n = 815)		
S/SE	5	406.03	1.23 (0.52-3.67)	8	471.82	1.65 (0.89-3.46)
Major bleeding	22	405.67	5.42 (3.60-8.53)	23	469.75	4.90 (3.48-7.11)

Abbreviations as in Table 2.

escalating drug exposure. Perhaps the remaining stroke risk is attributable to atheroembolic disease or other noncardioembolic stroke sources not readily addressed with systemic anticoagulation therapy. This observation illustrates the inflection point at which increased bleeding risk no longer justifies intensified anticoagulation therapy.

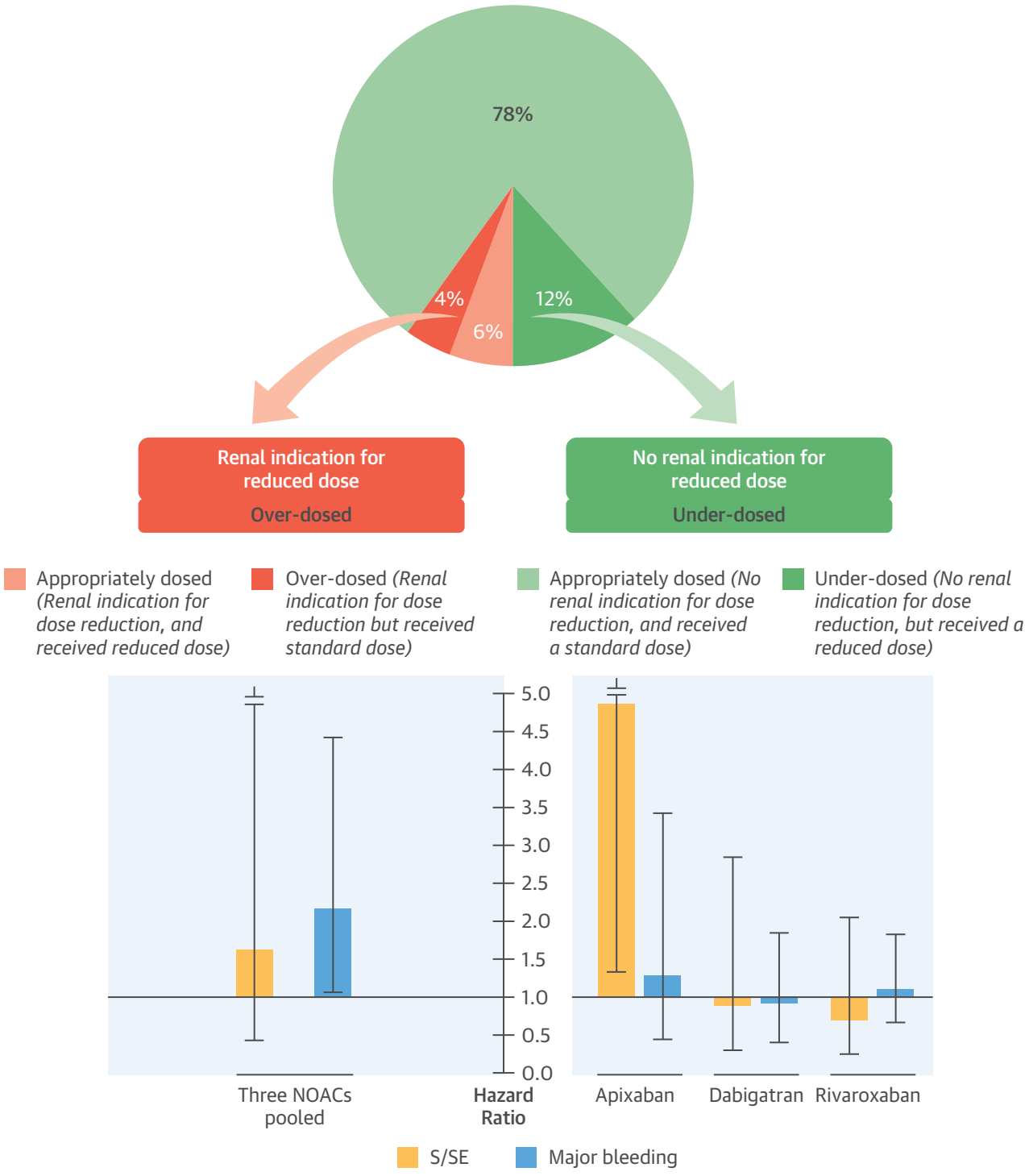
Among patients with no renal indication for dose reduction, the use of a reduced dose seemed to be more prevalent than what might be expected by extrapolation of the clinical trial data. The proportion of apixaban-treated patients receiving dose reduction without renal indication was 3.5-fold higher than in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (16.5% vs. 4.7%) (2). Because eGFR or creatinine is a continuous variable but the choice between a standard or reduced dose is binary, other

FIGURE 4 Outcomes Associated With Underdosing



Among patients without a renal indication for dose reduction, event rates for S/SE and major bleeding and hazard ratios comparing a reduced dose versus a standard dose non-vitamin K antagonist oral anticoagulant (potential underdosing effect) favored the standard dose. Abbreviations as in Figure 3.

CENTRAL ILLUSTRATION **Prevalence and Impact of Inappropriate NOAC Dosing**



Yao, X. et al. J Am Coll Cardiol. 2017;69(23):2779–90.

We investigated non–vitamin K antagonist oral anticoagulant (NOAC) dosing patterns and associated outcomes. Prevalence of inappropriate dosing as shown in the pie chart was defined according to baseline renal function. Overdosing was associated with a higher risk of major bleeding with the NOACs, whereas underdosing was associated with a higher risk of ischemic stroke or systemic embolism (S/SE) in the apixaban-treated patients (hazard ratios comparing inappropriate to appropriate dosing in propensity score–matched cohorts).

factors come into play for patients with renal function near the cutoff range for dose reduction, such as drug interactions and predicted bleeding risks. Furthermore, because anticoagulation is a preventative therapy, there is little positive reinforcement for appropriate dosing (strokes avoided) but ample opportunity to observe the harms of therapy (major and minor bleeding). This disconnect between tangible risks and intangible benefits might contribute to a tendency toward cautious but deliberate underdosing.

Potential underdosing (using reduced dose NOACs in patients without severe renal impairment) was associated with a nearly 5-fold increased risk of stroke in apixaban-treated patients. This outcome suggests that the tendency to prescribe reduced dose apixaban comes at the cost of reduced effectiveness of stroke prevention. Interestingly, such patients seemed to have bleeding rates comparable to those receiving a standard dose.

A similar underdosing effect was not seen in the dabigatran- and rivaroxaban-treated patients. The use of reduced dose rivaroxaban was associated with a nonsignificant trend toward lower stroke risk. This finding was consistent with a recent study using the Danish national database showing that reduced dose apixaban was associated with a trend toward higher risk of stroke, whereas reduced dose rivaroxaban exhibited a trend toward lower risk of stroke compared with warfarin (21). This finding begs the question: is the underdosing effect unique to apixaban or was the present study simply better powered to detect a difference in these patients? We cannot be certain, but it is likely that both explanations are true to some extent. First, the reduced dose of apixaban is one-half the standard dose (2.5 mg vs. 5 mg), whereas the reduced dose of rivaroxaban is 75% of the standard dose (15 mg vs. 20 mg). Second, the reduced dose of dabigatran approved by the FDA is 75 mg, not the 110-mg dose evaluated in the trial and approved in Europe. Thus, physicians may use this untested dose more cautiously. Third, the use of a reduced dose was more prevalent in apixaban-treated patients compared with dabigatran-treated patients (16.5% vs. 8.9%), making it easier to detect a difference. Lastly, apixaban-treated patients were older, with a mean age of 83 years, compared with 77 and 76 years in the dabigatran- and rivaroxaban-treated patients, respectively. Therefore, the stroke rate in patients receiving reduced dose apixaban was higher. Moreover, the stroke rate in the standard dose apixaban arm was particularly low. Although it is conjecture, it is likely that standard dose apixaban is highly effective in preventing stroke, particularly in this patient population with mild renal impairment (mean eGFR 60 ml/min/1.73 m^2), as shown in the pivotal trial (22).

STUDY LIMITATIONS. First, despite careful propensity score adjustment, there is always a possibility of residual confounding. However, we made every effort to match the groups on all foreseeable confounders and included as many as 50 dimensions. The test of falsification endpoints also provided some reassurance that there was no substantial residual confounding.

Second, the average follow-up was short, which is commonly seen in oral anticoagulant research using "real-world" data, particularly in the United States. Several recent NOAC studies reported a mean follow-up of ≤6 months (23–27). This outcome is likely due to poor adherence to treatment in routine practice (28) and thus does not necessarily limit the generalizability of our results. Furthermore, a short follow-up does not limit the usefulness of our findings to inform practice because patients taking NOACs should be seen by physicians at least once or twice a year to evaluate kidney function and the appropriateness of dosing. According to the guidelines (6), in the elderly (≥75 to 80 years of age) or otherwise fragile patients, renal function should be evaluated at least once every 6 months. If renal function is impaired, physicians could specify a recheck interval in number of months (e.g., CrCl/10). Therefore, physicians do not need to make long-term risk predictions for dosing effect; the outcomes within the next few months are the most relevant information. The mean follow-up time also varied among NOACs, ranging from 5.3 months for apixaban to 8.6 months for dabigatran. However, the follow-up time between matched reduced and standard dose arms in each matched cohort was very similar. We tested the potential impact by limiting the follow-up time to the first 6 months, and the results remained largely unchanged.

Third, we only abstracted the most recent SCr result before treatment initiation, which may not necessarily reflect patient kidney function during follow-up. However, for most patients, renal function was relatively stable. The eGFR only slightly decreased with a mean of −1.6 ml/min/1.73 m^2 compared with baseline eGFR, and 3% had a change in renal indication for dose reduction during follow-up. Furthermore, because patient weight was unavailable in the database, we used the CKD-EPI equation rather than the Cockcroft-Gault method to calculate eGFR. However, the CKD-EPI equation was found to be more accurate in assessing renal function than the Cockcroft-Gault method (29,30).

Fourth, we relied on creatinine level to define the renal indication for apixaban dose reduction, which could lead to an overestimation of overdosing and underdosing. For overdosing, all apixaban-treated patients with a renal indication had severe renal impairment. The mean eGFR was only 31 ml/min/1.73 m^2. Whether patients with such low eGFR but age <80 years should receive a reduced dose is debatable, as these patients were largely excluded from the pivotal trial (22). We considered these patients as having a renal indication for dose reduction because low body weight (the third criterion of apixaban dose reduction) is very prevalent in patients with severe renal impairment. Furthermore, the baseline characteristics, as well as the stroke and bleeding outcomes, were very similar between patients <80 or ≥80 years of age (Online Tables 15 and 16). For underdosing, a majority of the patients <80 years of age with no renal indication definitely lacked an indication for dose reduction. A minority of the patients ≥80 years of age with normal or mildly impaired renal function would have low body weight; therefore, the misclassification would not be substantial.

Lastly, the number of events and the event rates were low; therefore, the findings should be viewed as hypothesis-generating and need to be confirmed by future studies.

CONCLUSIONS

In routine clinical practice, the prescribed NOAC doses are often inconsistent with FDA labeling. These prescribing patterns may be associated with worse safety with no benefit in effectiveness in patients who have severe kidney disease and worse effectiveness with no safety benefit in apixaban-treated patients who have normal or mildly impaired renal function.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: To determine the appropriate NOAC dose, clinicians should carefully assess the patient's renal function and other factors. Deviations from the labeled dose may compromise safety in patients with severe renal impairment and effectiveness in those with preserved renal function.

TRANSLATIONAL OUTLOOK: More studies and better clinical decision support tools are needed to guide NOAC dosing, particularly in patients with renal impairment.

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KEY WORDS bleeding, dose, embolism, kidney disease, stroke

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this article.