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Original Research Article

PREDICTORS AND PREVALENCE OF INACCURATE DOSING OF DIRECT ORAL ANTICOAGULANTS

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Abstract: *The retrospective study was conducted in tertiary care hospitals from January 2022 to June 2022 to investigate predictors and prevalence of inaccurate dosing of DOACs. The study included patients who were prescribed and taking DOAC during their admission to the hospital or before admission. The study was conducted on a total of 200 patients. Dosing appropriateness was assessed by checking if it was consistent with the AHA guidelines. 42 (21%) patients had inappropriate dosing, 25 (59.5%) were overdosed, and 17 (40.4%) were underdosed. According to univariate analysis, older age, lower CrCl, higher HAS-BLED, CHA2DS2-VASc, CCI, and prescription before admission were significantly associated with inappropriate dosing. It is concluded that inappropriate dosing, particularly under-dosing, of DOAC occurs commonly during clinical practice. DOACs should be prescribed carefully in outpatient settings and patients with renal dysfunction.*

Keywords: Direct Oral Anti-Coagulants, Under Dosing, Overdosing

Introduction

Direct oral anticoagulants (DOACs) have revolutionized oral anticoagulant therapy. These are now first-line drugs for preventing systemic embolism and stroke (Ellenberger et al., 2018) and treating venous thromboembolism (Tran et al., 2019). They have similar efficacy and better safety profile than warfarin, and DOACs do not require therapeutic monitoring due to predictable pharmacokinetic action (Alberts et al., 2022). However, their dosing schedule depends upon age, renal function, and weight; if not taken into account, this can lead to inappropriate dosing and other complications (Berger et al., 2021). Evidence shows that inappropriate dosing occurs commonly during clinical practice (Chan et al., 2020; Ding et al., 2021). A recent study on bleeding complications reported that the prevalence of inappropriate dosing of DOACs was 22% (Chua et al., 2022). In the present study, we aim to investigate predictors and prevalence of inaccurate dosing of DOACs.

Methodology

The retrospective study was conducted in tertiary care hospitals from January 2022 to June 2022. The study included patients who were prescribed and taking DOAC during their hospital admission or before admission. Informed consent of the participants was taken. The ethical committee of the hospital approved the study.

Data including age, gender, weight, alcohol intake, comorbidities, usual medications, type and dose of DOAC, medications with possible drug reactions, concurrent anti-platelet medications, liver function, hemoglobin, and serum creatinine was collected. The Charlson Comorbidity Index (CCI) was used for assessing comorbidities. Creatinine clearance (CrCl) was used for assessing renal function. For admitted patients, serum creatinine measurement soon after starting DOAC was used for measuring CrCl; serum creatinine measurement closest to discharge was used for those taking medication before admission. The dosing appropriateness was assessed by checking if it was consistent with the American Heart Association (AHA) guidelines(Chen et al., 2020).

SPSS version 23.0 was used for data analysis. Descriptive data is presented as frequency and percentages or mean and standard deviation. Student's *t*-test was used for comparing continuous variables, and Fisher's exact test for comparing categorical variables. The association between study variables and inappropriate dosing was assessed through univariate logistic regression. Variables independently associated with inappropriate dosing were determined through multivariate logistic regression analysis. P value < 0.05 was considered statistically significant.

Results

The study was conducted on a total of 200 patients. The mean age of the participants was 71.5 ± 15.4 years, and 51% were female. 88 (44%) patients were prescribed DOAC upon admission, and 112 (56%) took these before the admission. 42 (21%) patients had inappropriate dosing, 25 (59.5%) were overdosed, and 17 (40.4%) were underdosed. Among 25 overdosed patients, 2 received rivaroxaban despite contraindications based on CrCl. Anticoagulation indications included VTE treatment (n=71, 45%) and nonvalvular atrial fibrillation (n=85, 53.7%). The characteristics of patients who received inappropriate and appropriate dosing are compared in Table I. Patients with inappropriate dosing had lower CrCl, higher HAS-BLED, CHA2DS2-VASc, and CCI.

Univariate and multivariate analyses are summarized in Table II. According to univariate analysis, older age, lower CrCl, higher HAS-BLED, CHA2DS2-VASc, CCI, and prescription prior to admission were significantly associated with inappropriate dosing. According to multivariate analysis, only prescriptions prior to admission and lower CrCl were significantly associated with inappropriate dosing; lower CrCl was only associated with underdoing. Prescription before admission had borderline significance only (P=.09). According to multivariate analysis, no independent variable had a significant association with overdosing.

Table I Comparison of baseline characteristics in patients treated appropriately and inappropriately with DOACs

	Appropriate doing (n=158)	**Inappropriate dosing (n=42)**	**P value**
Age			<.01
<75 years	85 (53.7%)	10 (23.8%)	
≥75 years	71 (44.9%)	34 (80.9%)	
Male gender	77 (48.7%)	21 (50%)	.30
Indications			.26
Stroke prevention	85 (53.7%)	26 (61.9%)	
➢ **VTE treatment**	71 (44.9%)	18 (42.8%)	
DOC			
➢ **Rivaroxaban**	102 (64.5%)	22 (52.3%)	.42
➢ **Apixaban**	38 (24%)	21 (50%)	.07
➢ **Dabigatran**	16 (10.1%)	1 (2.3%)	.28
CCI	2.75 ± 1.91	4.31 ± 1.43	<.01
Creatinine clearance	70.54 ± 16.80	54.41 ± 14.98	<.01
Prescription prior to admission	76 (48.1%)	35 (83.3%)	<.01
Concurrent use of anti-platelet	31 (19.6%)	6 (14.2%)	.53
Drug interaction	36 (22.7%)	10 (23.8%)	.81
History of bleeding	11 (6.9%)	4 (9.5%)	.75
HAS-BLED score	1.32 ± 1.05	2.14 ± 1.05	<.01
CHA_2DS_2-VASc score	3.16 ± 1.77	4.87 ± 1.61	<.01

Table II Predictors of Inappropriate Prescription

	Univariate regression			**Multivariate regression**		
	OR	**95% CI**	**P**	**OR**	**95%CI**	**p**
Age >75 years	5.4	2.31,12.11	<.01	1.82	.67,5.13	0.21
Male gender	.71	.36, 1.39	.31	-	-	-
Indication	.66	.34, 1.32	.21	-	-	-
CCI	1.55	1.29, 1.91	<.01	1.17	.88,1.53	.28
Creatinine clearance (low)	1.05	1.02,1.07	<.01	1.05	1.02,1.08	<.01
Prescription prior to admission	5.76	2.42,13.71	<.01	2.61	1.02,6.77	.045
Concurrent use of anti-platelet	.77	.31, 1.87	.52	-	-	-
Drug interaction	1.11	.52, 2.31	.82	-	-	-
History of bleeding	1.22	.35, 4.10	.75	-	-	-
HAS-BLED score	1.98	1.42, 2.73	<.01	-	-	-
CHA_2DS_2-VASc score	1.65	1.32, 2.01	<.01	-	-	-

Discussion

The study showed inappropriate dosing is significantly associated with prescription prior to admission and impaired renal function. Moreover, impaired renal function is correlated with both over and under-dosing. Different international studies have examined the prevalence of inappropriate dosing of DOACs. According to these studies, prevalence varies between 14% and 38% (De Vincentis et al., 2023; Diaz et al., 2021). The different study methodologies can explain the variation in prevalence rates. For instance, a study reported a prevalence rate of 35%(Ding et al., 2021). This study used product information to determine dose appropriateness for rivaroxaban and dabigatran. They also used higher serum creatinine at admission than discharge to assess dose appropriateness in patients prescribed DOACs before admission. In another study, the prevalence of inappropriate

dosing was 28.7% (Li et al., 2022). They included patients who were prescribed DOACs for stroke prevention. Moreover, the majority of patients were given apixaban.

The current study shows that underdosing is more prevalent than overdosing. A previous study also reported similar results and showed that 79% of cases prescribed DOACs for stroke prevention were underdiagnosed (Li et al., 2022). Other studies showed similar trends and evidence suggesting that prescribers are mostly fearful of bleeding complications that lead to underdosing (Bhat et al., 2023). Moreover, prescribers may use different guidelines. For instance, according to TGA guidelines, apixaban is contraindicated when CrCl < 25, while in AHA guidelines, it can be given if the patient has CrCl < 15 and is on dialysis.

The results of our study suggested an association between inappropriate dosing and impaired renal function, in line with the previous literature (Pharithi et al., 2019; Zhang et al., 2020). However, the association with overdosing was only due to a powered study. Due to the retrospective design, this study does not investigate the cause of the association between inappropriate dosing and impaired renal function. Few studies show moderate impairment is more frequently associated with inappropriate dosing than mild or severe impairment (Moudallel et al., 2018; Steinberg et al., 2016). The current report shows that prescription prior to admission is more likely associated with inappropriate dosing. Similar results are reported by the previous studies (Moudallel et al., 2018; Shen et al., 2021). Moreover, studies also show that DOAC prescription in outpatient settings is more frequently associated with inappropriate dosing than inpatients (Miyazaki et al., 2020). This is because there is less vigorous estimation of real function in an inpatient setting. In the current study, the treatment of the majority of patients was initiated in an outpatient setting. However, the exact setting of the initial prescription was not verified.

Studies have reported between inappropriate DOAC dosing and different variables like older age (Sugrue et al., 2021), anticoagulation for stroke prevention (Sugrue et al., 2021), female gender (Sugrue et al., 2021), higher HAS-BLED, CHA_2DS_2-VASc scores and choice of drug (Miyazaki et al., 2020). The current study reported univariate or borderline multivariate association. This may be because of the limited power of the study; studies with adequate statistical power are recommended for more evaluation.

Conclusion

Inappropriate dosing, particularly under-dosing, of DOAC occurs commonly during clinical practice. DOACs should be prescribed carefully in outpatient settings and patients with renal dysfunction.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned.

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

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