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ORIGINAL ARTICLE

Quality of clinical direct oral anticoagulant prescribing and identification of risk factors for inappropriate prescriptions

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Aims: Even though the use of direct oral anticoagulants (DOACs) is safe based on clinical outcomes, drug safety also depends on appropriateness of drug prescription, which is challenging for DOACs since many patient factors need to be considered. The aim of this study was to assess the appropriateness of DOAC prescriptions and to identify risk factors of determinants for inappropriate DOAC prescriptions.

Methods: A retrospective study in a nonuniversity teaching hospital was performed of hospitalized patients (≥18 years) who received an initial DOAC prescription between February and August 2018. Appropriateness of prescribing was evaluated on 8 criteria by using a modified version of the medication appropriateness index.

Results: A total of 770 initial DOAC prescriptions of inpatients were evaluated: 267 patients (34.6%) had at least met 1 inappropriate criterion for a DOAC prescription. The most frequent inappropriate criterion was dosage (17.4%). Of the 4 DOACs, dabigatran (21.6%) and apixaban (21.2%) were mostly inappropriate dosed. In a multivariable analysis, reduced renal function (estimated glomerular filtration rate <50 mL/min; odds ratio [OR] = 2.35; $P < .001$), a diagnosis of atrial fibrillation (OR = 1.87; $P = .004$), and 'prescribed by surgeons' (OR = 1.9; $P = .013$) were independently associated with inappropriateness of prescribing.

Conclusion: This study has highlighted a high degree of inappropriate prescribing of DOACs. These results underline the need for targeted interventions to improve DOAC prescribing.

KEYWORDS

appropriateness of prescription, DOAC, medication appropriateness index, medication errors, prescribing patterns

1 | INTRODUCTION

Oral anticoagulants such as direct oral anticoagulants (DOACs) are highly effective for the prophylaxis and treatment of venous thrombosis in both nonvalvular atrial fibrillation and venous thromboembolism.[1–3] Meta-analyses of randomized clinical trials show that DOACs have a lower all-cause mortality compared to vitamin K antagonists (VKAs), which is primarily driven by a lower incidence of fatal intracranial haemorrhages.[4–6] However, the use of DOACs is still associated with increased bleeding risk and these drugs are therefore considered as high risk medication.[7]

Even though the use of DOACs is safe based on clinical outcomes, drug safety also depends on appropriateness of drug

The protocol was evaluated and approved by the Institutional Review Board of the St. Antonius Hospital (Utrecht/Nieuwegein, protocol number R&D/Z18.060). No written informed consent was required since only previously collected information was analysed. Individual patient data were documented anonymously.

This study did not performed interventions with patients. There is no principal investigator.

prescription, which is challenging for DOACs. For instance, different patient characteristics (such as age, weight, renal and hepatic function, and comedication) have to be taken into account to determine the right dosage and there are different indications with subsequent multiple dosing regimens to be considered, thereby potentially introducing a risk of inappropriate prescription.

Appropriate prescribing of DOACs is a topic of interest given their increasing use. An evaluation of the appropriateness of prescribing the 4 DOACs has not yet been performed. The main objective of this retrospective study is to assess the appropriateness of DOAC prescriptions of hospitalized patients in a Dutch teaching hospital and to identify both patient- and process-related factors that are associated with inappropriate DOAC prescribing.

What is already known about this subject

- Drug safety depends on the appropriateness of the prescription, which is challenging for DOACs since different patient factors needed to be considered.
- Inappropriate DOAC prescribing might lead to serious drug-related problem such as bleeding or thrombotic events.

What this study adds

- More than 1/3 of the patients had an inappropriate DOAC prescription. Apixaban and dabigatran were mostly inappropriately dosed.
- A reduced renal function, diagnosis of atrial fibrillation and prescribed by surgeons were independently associated with inappropriate DOAC prescription.
- Educational interventions and multidisciplinary hospital teams are needed to improve appropriate DOAC prescribing.

2 | METHODS

2.1 | Design, setting and participants

A retrospective, observational cohort study was conducted at a large nonuniversity teaching hospital (St. Antonius Hospital, The Netherlands). Inpatients of 18 years and older at the time of admission with a documented prescription for **apixaban**, **dabigatran**, **edoxaban** or **rivaroxaban** between 15 February and 15 August 2018 were selected. Patients who had a documented DOAC prescription in the current hospital prior to the index date were excluded. This study protocol was approved by the MEC-U Medical Ethics Committee. No written informed consent was required.

2.2 | Data collection

Only the first DOAC prescription for each patient, which was not (yet) intervened by the clinical pharmacy as part of the drug safety monitoring system, was selected for review. The electronic medical record of each patient was reviewed manually. A detailed medical status was obtained, which included patient characteristics, clinical diagnoses and prescription and prescriber characteristics (Table 1). The most recent required laboratory results near the DOAC prescription date were included in the study and were considered eligible if they were measured within 1 month of the initial DOAC prescription date. Patient-related factors were defined by sex, age, body mass index, estimated glomerular filtration rate (eGFR) and comorbidities. Process-related factors included prescription (initiation in current hospital or elsewhere, type of DOAC, indication) and prescriber characteristics (medical specialty and degree of prescriber).

2.3 | Appropriateness of prescribing

Appropriateness of DOAC prescribing was scored using the medication appropriateness index (MAI), a comprehensive tool designed to evaluate (in)appropriate prescribing on several criteria.[8,9] Each DOAC prescription was scored based on 9 criteria: indication, choice, duration, dosage, modalities of administration, practicability of administration, drug–drug interactions, drug-disease interactions and therapeutic duplication. However, the MAI tool was slightly modified since correct and practical administration could not be assessed from the medical records. Instead of these criteria, an extra criterion was added: *required laboratory tests prior at initiation available.* Explicit instructions for the MAI tool were developed to determine the appropriateness of a DOAC prescription (see Supporting Information Appendix). For each criterion a score was given: A (appropriate), B (inappropriate with limited clinical importance), C (inappropriate) or Z (insufficient information to evaluate appropriateness). A-rating was defined as according to the summary of product characteristics (SmPC), European[10,11] or national guidelines.[1,2] C-rating was defined as not according to SmPC or the guidelines. B-rating was defined as marginally appropriate where caution is recommended and there is no formal contraindication or clear guideline recommendation yet.[12] With regards to dosing, an inappropriate DOAC dosage was defined as a dose that is not in agreement with the SmPC. Underdosing and overdosing were respectively defined as a lower or higher dose than the SmPC recommendations.

An additional dosage analysis for atrial fibrillation (AF) patients was performed that took into account the use of antiplatelet therapy and the HAS-BLED score according to the European Society of Cardiology (ESC) and the European Heart Rhythm Association (EHRA) guidelines.[10,11] The ESC guideline takes into consideration that when a DOAC is used in combination with antiplatelet therapy the lowest approved effective dose should be considered. In addition, the EHRA 2013 guideline recommends that if concomitant antiplatelet therapy is indicated, a lower dose of DOAC might be a safer option especially in patients with a HAS-BLED score of ≥3.

TABLE 1 Patient, prescription and prescriber characteristics

	All patients (*n* = 770) *n* (%)
Patient characteristics	
Female	349 (45.3)
Age (y), median (range)	74 (23–97)
- >75 y	350 (45.5)
BMI (kg/m^2), median (range)	26: 14–53
- Normal weight (BMI 18.5–25)	218 (28.3)
- Underweight (BMI ≤18.5)	30 (3.9)
- Overweight (BMI 25–30)	302 (39.2)
- Obesity (BMI ≥30)	169 (21.9)
- n/a	51 (6.6)
eGFR (mL/min), median (range)	71 (12–90)
- CrCl ≥50 mL/min	564 (73.2)
- CrCl 30–50 mL/min	144 (18.7)
- CrCl 15–30 mL/min	39 (5.1)
- CrCl ≤15 mL/min	2 (0.3)
- n/a	21 (2.7)
Clinical diagnoses	
- Heart failure	128 (16.6)
- Hypertension	404 (52.5)
- Diabetes mellitus	181 (23.5)
- Previous stroke/TIA	119 (15.5)
- Vascular disease[aa]	239 (31)
- Previous bleeding or predisposition (anaemia)[bb]	108 (14)
- Liver disease[bb]	21 (2.7)
- Active malignancy	99 (12.9)
- Bariatric surgery	16 (2.2)
Prescription characteristics	
Initiated during current admission	410 (53.2)
Type of DOAC	
- Apixaban	312 (40.5)
- Dabigatran	51 (6.6)
- Edoxaban	21 (2.7)
- Rivaroxaban	386 (50.1)
Indication	
- Atrial fibrillation	545 (70.8)
CHA_2DS_2-VASc (mean ± SD)	3.6 ± 1.6
HAS-BLED (mean ± SD)	1.7 ± 0.98
- VTE treatment or prophylaxis	207 (26.9)
- Other	11 (0.8)
- N/A	7 (0.9)
Prescriber characteristics	
Medical specialty	
- Cardiology	204 (26.5)
- Neurology	72 (9.4)
- Surgery	112 (14.5)
- Internal medicine	353 (45.6)
- Other	29 (3.8)
Medical degree	
- Resident	573 (74.4)
- Specialist	171 (22.2)
- Nurse specialist	26 (3.4)

BMI, body mass index; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate based on CKD-EPI formula; SD, standard deviation; VTE, venous thromboembolism; n/a = information not available in medical record.

[a]Definition according to CHA_2DS_2-VASc criteria.

[b]Definition according to HAS-BLED criteria.

2.4 | Outcome measures and data validation

The primary outcome measure was to measure the prevalence of inappropriate DOAC prescriptions. An inappropriate DOAC prescription was defined as the proportion of patients with ≥1 inappropriate criterion. If a patient was rated inappropriate for indication then choice, duration and dosage were also rated inappropriate according to the instructions of the MAI-tool. The number of inappropriate criteria was counted independently. Only inappropriate rating C was considered for the primary outcome. The secondary outcome measure was to identify patient- and process-related factors that are associated with inappropriate prescribing. To minimize for bias, we have programmed codes in REDCAP to evaluate the appropriateness of each criteria. Moreover, a random sampling of prescriptions was taken to verify the outcome of the programmed codes. In addition, uncertain outcome measurements were re-evaluated by a clinical pharmacist.

2.5 | Analysis

Patient data were analysed with SPSS V.24.0 (IBM, New York, USA). Descriptive statistics were used to describe baseline characteristics and outcomes. A binary multivariable logistic regression was performed to identify patient- and process-related factors associated with the primary outcome. A pre-selection of risk factors with a *P*-value of <.15 in the univariable analysis was selected as candidate for the multivariable model. Regardless of the outcome of the univariable tests, age and sex were always included in the multivariable regression analyses. The group within a categorical variable that represented the majority was chosen as a reference. With the exception of the variable *medical specialty of the prescriber*, cardiology was chosen as reference. Ratings A, B were dummy coded as appropriate and C-rating as inappropriate prior to regression analysis. Z-ratings were not included in the regression analysis. A *P*-value <.05 was considered to be statistically significant.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to pharmacology.

3 | RESULTS

A total of 770 patients were included in this study. Rivaroxaban was the most frequently prescribed drug (50.1%), followed by apixaban (40.5%), dabigatran (6.6%) and edoxaban (2.7%). Prevention of stroke and systemic embolism in AF was the most prevalent indication for prescribing a DOAC, accounting for 545 (70.8%) patients. Patient, prescription and prescriber characteristics are summarized in Table 1.

3.1 | Prevalence of inappropriate prescriptions

Out of the 770 patients included in the analysis, 267 (34.6%) patients had at least met 1 inappropriate criterion for a DOAC prescription. The most common inappropriate criterion was *dosage* (17.4%). Figure 1 describes the frequency of inappropriateness per criterion.

3.2 | Dosage

In the present analysis, 579 (75.2%) patients were prescribed an appropriate dose, 134 (17.4%) had an inappropriate dose and 7.4% of the dosages were not assessable as a result of incomplete documentation of parameters such as eGFR, indication, or weight while using apixaban. Overall, most of the inappropriate doses were observed for dabigatran (21.6%) and apixaban (21.2%) followed by edoxaban (14.3%) and rivaroxaban (14%). The reasons for inappropriate dosing were not adjusting the dose based on the number of criteria for dose reduction (44.8%), not adjusting for renal insufficiency (35.8%), wrong frequency (17.9%) and the presence of contraindications (1.5%). Out of those scored as *inappropriate dosage*, a total of 77 (57.5%) patients received a lower dose than the manufacturer recommendations and 57 (42.5%) patients had a higher dose. Patients treated with apixaban (n = 42, 63.6%) and dabigatran (n = 9, 81.8%) were more often underdosed than overdosed. On the contrary, patients prescribed with edoxaban (n = 2, 66.6%) and rivaroxaban (n = 29, 53.7%) were more often overdosed than underdosed. The most frequent reason for inappropriate dosage for apixaban was that AF patients were prescribed with the reduced dose, despite only meeting 1 criterion for dose reduction.

The additional dosage analysis of AF patients with a CHA_2DS_2-VASc score of at least 1 (n = 512), showed that 394 patients (77%) had an appropriate dose according to the SmPC (Table 2). If the use of

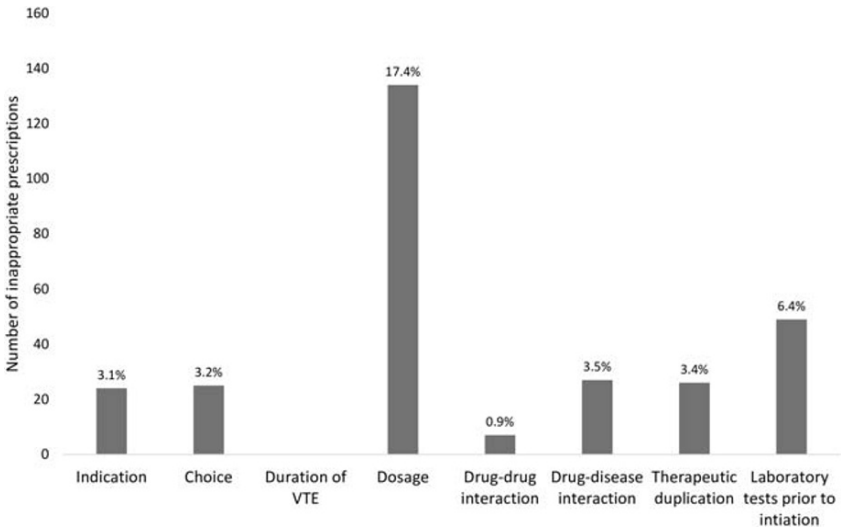

FIGURE 1 Number of inappropriateness prescriptions per independent criterion. VTE, venous thromboembolism

TABLE 2 Inappropriate dose for atrial fibrillation (AF) patients according to the summary of product characteristics (SmPC) and European guidelines.[10,11]

Dose adjustment should be considered in case:	According to guideline	Appropriate dose (n)	Inappropriate dose (n)	
			Overdosed	Underdosed
PC	SmPC	394 (77%)	51 (10%)	67 (13%)
PC + TAR	ESC AF 2016	332 (65%)	130 (25%)	50 (9.8%)
PC + TAR + HASBLED≥3	EHRA AF 2013	369 (72%)	83 (16%)	60 (12%)

PC = patient characteristics require dose reduction (renal function, body weight and/or age), TAR = concomitant.
ESC, European Society of Cardiology; EHRA, European Heart Rhythm Association

antiplatelet drugs and the HAS-BLED score were taken into consideration according to the ESC and EHRA guidelines, then 332 (65%) and 369 patients (72%) were considered appropriately dosed, respectively. In line with the SmPC, 67 patients (13%) were underdosed and according to the ESC and EHRA guidelines the percentage of underdosing was 10 and 12%, respectively. In contrast, 51 patients (9.8%) were overdosed according to the SmPC. In agreement with the ESC and EHRA guidelines, 25 and 16% of the patients were overdosed, respectively.

3.3 | Risk factors associated with inappropriate DOAC prescription

Three significant independent predictors were identified in the multivariable regression for the outcome of inappropriate prescription: decreased renal function (eGFR <50 mL/min/1.73m^2), the diagnosis of AF and the medical specialty of the prescriber (Table 3). Patients with decreased renal function had higher odds of inappropriate DOAC prescribing compared to those with an eGFR >50 mL/min/1.73m^2 (odds ratio [OR] = 2.35; 95% confidence interval [CI] 1.61–3.45; P < .001). Furthermore, the OR for an inappropriate DOAC prescription in patients with AF compared to patients without AF was 1.87 (95% CI 1.22–2.87 P = .004). The third significant predictor was medical specialty of the prescriber. Patients in which DOACs were prescribed by surgeons had an increased risk of having an inappropriate DOAC prescription compared to those who received a prescription from cardiologists (OR = 1.90; 95% CI 1.14–3.20; P = .013).

4 | DISCUSSION

This study illustrates that inappropriate prescribing of DOACs is frequent among inpatients, presumably resulting in an altered benefit–

TABLE 3 Logistic regression inappropriate direct oral anticoagulant (DOAC) prescription

	Inappropriate DOAC prescription					
Risk factor	Univariable			Multivariable		
Patient related factors	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Female sex	0.95	0.71–1.29	.76	0.90	0.64–1.25	.52
Age > 75 y	1.17	0.87–1.58	.31	0.92	0.65–1.30	.64
Overweight/obesity	1.17	0.85–1.63	.34			
eGFR <50 mL/min	2.34	1.66–3.29	*<.001*	2.35	1.61–3.45	**<.001**
≥1 comorbidity[a]	1.38	0.94–2.04	*.10*			
≥2 comorbidities[a]	1.29	0.96–1.74	*.10*			
≥3 comorbidities[a]	1.30	0.89–1.88	.18			
Process-related factors						
Initiation in current hospital	1.08	0.80–1.46	.61			
Atrial fibrillation	2.17	1.51–3.12	*<.001*	1.87	1.22–2.87	**.004**
Type of DOAC			.001			
Rivaroxaban	1.00					
Apixaban	1.87	1.36–2.57	<.001			
Dabigatran	2.50	1.11–3.77	.021			
Edoxaban	1.21	0.48–3.08	.69			
Medical specialty			<.001			.002
Cardiology	1.00					
Neurology	1.38	0.79–2.40	.26	1.73	0.97–3.09	.063
Surgery	1.49	0.93–2.41	.10	1.91	1.14–3.19	.013
Internal medicine	0.62	0.43–0.89	.010	0.83	0.56–1.25	.38
Degree			.01			
Resident	1.00					
Specialist	1.42	0.99–2.03	.05			
Nurse specialist	0.70	0.29–1.68	.42			

[a]Hypertension, heart failure, diabetes mellitus, previous stroke or TIA, vascular disease, cancer and liver disease were included in the variable comorbidity.
CI, confidence interval; OR, odds ratio.
Italic: relaxed P < .15; **Bold**: P < .05.
Hosmer and Lemeshow test P = .733

risk ratio for these patients. To the best of our knowledge, this is the first study evaluating the appropriateness of prescribing the 4 DOACs with the MAI-tool.

More than 1/3 (34.6%) of the patients had at least 1 inappropriate criterion for a DOAC prescription. It is known from previous studies that prescribing DOACs appropriately is challenging, since different patient factors need to be considered. Our results are in the range with previous findings that also used the MAI tool (31–60%) to evaluate apixaban, dabigatran and rivaroxaban prescriptions.[13–15] However, there are some notable differences between the previous studies and the current study, which makes comparison of the results challenging. Firstly, this study included patients with a prescription for any DOAC, irrespective of indication, while the previous studies only captured 2 or 3 DOACs for AF mostly. Secondly, the results may vary due to different study designs and the different types of hospital settings. Furthermore, the definitions of the criteria in the MAI tool varied between the studies and a modified MAI tool was used in the present study. To clarify, the criterion *choice* was not scored inappropriate among patients with extreme bodyweight (<50 kg and >110–120 kg) in this research and previous studies.[13,15] The reason for this is the lack of evidence in guidelines and the fact that the SmPC does not specify dosing solely on weight. Only in the study of Larock *et al*. was the criterion *choice* classified as inappropriate in patients with extreme bodyweights.[14] In our opinion, further studies are needed to clarify whether DOACs are inappropriate in patients with extreme bodyweights.

Regarding dosing of DOACs, incorrect dosing varied from 15 to 34% in previous studies.[13–22] Our study confirms these findings since 17.4% of the patients had been prescribed an inappropriate dose. The main reasons for incorrect DOAC dosing were not adjusting the dose based on the number of criteria for dose reduction or not adjusting the dose correctly for the current renal function. This includes dose reduction despite adequate renal function as well as lack of dose adjustment for reduced renal function. Previous studies showed that apixaban was more often inappropriately dosed compared to dabigatran and rivaroxaban.[23,24] In our study, apixaban and dabigatran were more frequently inappropriately dosed compared to rivaroxaban. A possible explanation for this is that apixaban and dabigatran have more complex dose adjustment criteria than rivaroxaban. For example, to determine the dosage of dabigatran, a prescriber needs to evaluate the age as well as the use of concomitant other drugs with a known drug–drug interaction with dabigatran (e.g. verapamil). For apixaban, 3 criteria have to be taken into account (age, weight and renal function) and dose reduction only applies for patients who meet a minimum of 2 of these criteria. A recent study showed that underdosing is the most common drug-related problem for inappropriate DOAC prescribing when using the SmPC as reference.[24] We also observed the same finding in our study. A possible explanation of underdosing is that physicians rather prescribe the reduced DOAC dose due to the bleeding risk.

The use of antiplatelet agents in combination with anticoagulants or high HAS-BLED scores is associated with a significant higher risk of major bleeding and therefore a lower DOAC dose is recommended by the European guidelines for AF patients.[10,11] The additional dosage analysis took into consideration that physicians might have prescribed a reduced dose due to concomitant use of an antiplatelet drug and/or a high HAS-BLED score. According to the SmPC, ESC and EHRA guidelines, the percentage of (potentially) overdosed patients was 10, 25 and 16%, respectively, which could be potentially dangerous since it could lead to an increased bleeding risk.[25,26] Regarding our data, the percentage of underdosed patients was 13% according to the SmPC and decreased to 9.8 and 12% following ESC and EHRA guidelines, respectively. This decrease could be explained by the fact that patients may have an intentionally reduced DOAC dose due to presence of concomitant antiplatelet therapy and/or a high HAS-BLED score. Therefore, we agree with Moudallel *et al*. that EHRA and ESC guidelines are less strict and more practical to use in daily practice compared to the SmPC.[24] It is important to take into consideration not only the bleeding risk, but also the risk of thrombotic events since DOAC dose reduction could also lead to underexposure with an (relative) increased risk of thrombotic events.[26]

These results underline the complexities for prescribers to find the optimal dose and balance between reducing thromboembolic risk and bleeding risk in the individual patient. Another concerning finding was that DOACs were also prescribed to patients in whom the safety and effectiveness has not been demonstrated yet. For example, DOACs were prescribed in patients who had undergone bariatric surgery (2.2%) while there is currently insufficient information on gastrointestinal absorption of DOACs in these patients.[27]

According to the multivariable regression analysis, patient-related risk factors of inappropriate prescription were decreased renal function and the diagnosis of AF. The process-related risk factor associated with inappropriate prescription was the medical specialty of the prescriber. Compared to cardiologists, surgeons had a significantly higher chance of prescribing an inappropriate DOAC prescription. This may be due to the fact that cardiologists are more focused on prescribing anticoagulation and are therefore more aware of the current guidelines for managing anticoagulation therapy than surgeons. A recent Canadian study among physician residents, pharmacists and nurse practitioners from various medical departments showed that there was lack of knowledge about the safe and effective use of DOACs.[28] It is therefore crucial to improve the knowledge of prescribers about DOACs with educational interventions to enhance patient safety. Miele *et al*. showed that implementing a pharmacist driven DOAC protocol significantly improved appropriate DOAC prescribing. This protocol was implemented to educate clinical pharmacists.[29] Therefore, educational trainings could also be useful to improve DOAC prescribing for other health care professionals. Another effective method is by having a multidisciplinary collaborative in-hospital team (consisting of clinical pharmacists and haematology specialists) that review and consult regarding anticoagulation therapy.[30] A multidisciplinary team can also contribute valuably to promote safe and responsible use of DOACs, since an adequate coagulation drug safety monitoring system contains clinical (risk of bleeding) and pharmaceutical (dosage, administration, interactions) evaluations. In addition, to prevent some of the prescribing errors,

dosing alerts or clinical decision support tools are important to be incorporated in the computerized physician order entry system, which takes into account patient characteristics for dose adjustments.[23]

The strengths of our study are the large sample size and the fact that all available DOACs were included irrespective of indication. In addition, we assessed the *real* rate of prescribing errors, because we only reviewed the initial DOAC prescription. However, the present study should be viewed in the context of several limitations. Firstly, in this study we only included potential and relevant risk factor for inappropriate DOAC prescription based on previous findings in the literature.[13–15] Secondly, relatively few of patients were prescribed edoxaban, which made it difficult to put the results of edoxaban into perspective. Thirdly, due to the retrospective study design, we had to rely on the data that already had been collected in the medical record. Based on this, our results may be confounded by incomplete documentation. Lastly, the external validity is limited due to the single-centre study design. It would be useful to complement our data in a multicentric cohort, which also allows the hospitals to compare appropriateness of DOAC prescribing.

5 | CONCLUSION AND RELEVANCE

It is essential to ensure safe and appropriate use of DOACs, since inappropriate DOAC prescribing might lead to serious drug-related problems. The evaluation of the quality of prescribing DOACs shows that in up to 1/3 of all patients DOACs are prescribed inappropriately. This study reminds prescribers to remain vigilant when prescribing DOACs and these results clearly underline the need for educational interventions and multidisciplinary hospital teams.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Z.Z., M.B. and M.S. designed the study. Z.Z. collected the data and Z.Z., M.B. and E.G. analysed the data. Z.Z., M.B., M.S., A.H. and E.G. interpreted data. Z.Z. drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript version.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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