Assessment and predictors of inappropriate dose of direct oral anticoagulants

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ABSTRACT

Direct-Acting Oral Anticoagulants (DOACs) have revolutionized the management of Atrial Fibrillation (AF) and Venous Thromboembolism (VTE). However, recent audits reveal a significant burden of inappropriate dosages in the prescribing of direct-acting oral anticoagulants. Our aim is to identify the prevalence and predictors of such inappropriate dosing in our patients. This retrospective study was conducted from June 2016 to January 2018. Patients who received dabigatran, rivaroxaban, or apixaban for treatment of venous thromboembolism or atrial fibrillation were included. Appropriateness of direct-acting oral anticoagulants dosing was assessed using US Food and Drug Administration guidelines. Data was analyzed using IBM® SPSS Version 26. 337 patients were included, with a mean age of 62.9±18.7 years. The majority were female (196, 58.3%). Of the patients, 194 (57.6%) received apixaban, 99 (29.4%) received rivaroxaban, and 44 (13.1%) received dabigatran. A total of 242 (71.8%) patients were prescribed direct-acting oral anticoagulants appropriately. Under-dosing and over-dosing were identified in 74 (22%) and 21 (6.2%) patients, respectively. Predictors of inappropriate dosing were age greater than 75 years (OR: 2.76, 95% CI: 1.67-4.56, p<0.001) and creatinine clearance less than 50 ml/minute (OR: 0.38, 95% CI: 0.19-0.74, p: 0.005). Inappropriate dosing was significantly associated with mortality (p=0.010).One-third of our patients received an inappropriate dose of direct-acting oral anticoagulants, mostly from under-dosing. Elderly age and low creatinine clearance are significant predictors of inappropriate dose administration.

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Introduction

For years, Low Molecular Weight Heparin (LMWH) and Vitamin K Antagonists (VKAs) were the main options available for anticoagulation in patients with thromboembolic disease and Atrial Fibrillation (AF). However, there were several obstacles to the long-term administration of these drugs. LMWH is available only in injectable form, making it difficult to use, which creates issues with patient compliance.[1] VKAs such as warfarin have many adverse effects, drug interactions, and a narrow therapeutic index, and they require regular monitoring.[2]

In the last decade, the introduction of Direct-Acting Oral Anticoagulants (DOACs) has led to a paradigm shift in the routine practice of anticoagulation therapy. These medications are also known as Non-Vitamin K Antagonist oral anticoagulants. They include factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, as well as the direct thrombin inhibitor dabigatran.[3] In October 2010, dabigatran etexilate became the first DOAC to receive approval from the US Food and Drug Administration (FDA). DOACs offer the advantage of oral administration, fewer drug interactions, and predictable pharmacodynamic response without the need for regular laboratory monitoring.[4] They are also associated with a reduced risk of mortality and major bleeding complications as compared to VKAs.[5]

The safety and efficacy profiles of DOACs are well established in the prevention and management of Venous Thromboembolism (VTE), which includes Deep Vein

Thrombosis (DVT) and Pulmonary Embolism (PE).[6] DOACs are also used as a first-line treatment to prevent cerebrovascular complications in patients with non-valvular atrial fibrillation, demonstrating superior outcomes as compared to VKAs.[7]

The prescription of DOACs is based on several factors, such as indication, age, Body Mass Index (BMI), concurrent medications, and renal and hepatic function.[8] For patients, DOACs have provided simplicity of use with minimal risks. However, due to their relatively new introduction in clinical practice, it has recently come to light that physicians may not be prescribing DOACs in an appropriate manner.[9]

Guidelines regarding the recommended administration of DOACs have been issued by organizations such as the FDA, the European Heart Rhythm Association (EHRA), and the International Society on Thrombosis and Hemostasis (ISTH).[10,11] However, recent audits of DOAC usage have highlighted a significant burden of inappropriate prescription of DOACs by physicians.[12] This inappropriate dosing includes over-dosing, under-dosing, and lack of dose adjustment according to renal impairment.[13] Such practices potentially put the patient at risk for various complications, which include major bleeding episodes and recurrence of thrombosis.[14] Administering non-recommended doses of DOACs is also associated with an increased rate of mortality, mainly due to cardiovascular complications.[15]

Therefore, the objective of this study is to assess the prevalence of inappropriate dosing of DOACs at a secondary care hospital in Riyadh, Saudi Arabia. We also aim to identify the factors associated with inappropriate dosing of DOACs in our patient population. We hope that our study will be able to identify existing gaps in clinical practice and provide the foundation for improving DOAC administration in the future.

Materials and Methods

This retrospective study was conducted at a secondary care hospital located in Riyadh, Saudi Arabia. Patients who presented for the treatment of documented non-valvular AF or radiologically proven VTE from June 2016 to January 2018 were identified retrospectively through the electronic health records system. Adult patients who received therapeutic doses of the DOACs rivaroxaban, dabigatran, or apixaban were included in this study. We excluded those patients who received only prophylactic doses of DOACs for VTE prevention.

Appropriateness of DOAC dosing was determined based on guidelines provided by the FDA, which are available in the package inserts of these medications.[16-18] Initial starting dose after the episode of VTE referred to the initiation of the DOAC treatment in the acute stage, where the dose needs to be higher in the cases of rivaroxaban and apixaban or preceded by LMWH in the case of dabigatran. Maintenance dose referred to maintenance therapy with DOAC, while the overall dosing regimen referred to both starting and maintenance therapy. Starting and maintenance doses were calculated for apixaban and rivaroxaban but not for dabigatran, which has a fixed dose. Follow-up data was collected from the time of anticoagulation initiation to the last encounter date, death, or the end of the study period. Data was collected from the electronic medical charts with the aid of a structured proforma. Doses were classified as appropriate, inappropriately low, or inappropriately high based on an analysis of patient medical records by a qualified thrombosis specialist.

Baseline CHADS score was determined to assess the initial need for anticoagulation in patients with AF. This score is assigned after assessing the patient's age, presence of congestive heart failure, hypertension, diabetes mellitus, and history of stroke.[19] A score of ≥1 in males or ≥2 in females is an indication for initiation of anticoagulation therapy.

The HAS-BLED score was also used to assess the risk of bleeding as an adverse effect of using anticoagulation in these patients. This score integrates the impact of hypertension, abnormal liver or kidney function, history of stroke or bleeding, labile International Normalized Ratios Of Prothrombin Time (INRs), elderly age, and drugs and alcohol on the occurrence of hemorrhagic complications.[20] A HAS-BLED score of ≥3 indicates that a patient on anticoagulation is at risk of bleeding.

As DOACs require dose adjustment for renal impairment, creatinine clearance was determined using the Cockcroft Gault formula, which utilizes patient age, gender, weight, and serum creatinine levels.[21]

Data was entered and analyzed using the Statistical Package for Social Sciences, IBM® SPSS Version 26. Mean and standard deviation were reported for quantitative variables such as age and creatinine clearance, whereas frequencies and percentages were reported for qualitative variables, including gender, diagnosis, co-morbidities, and DOAC regimen. Univariate and multivariate regression analysis was performed to identify the predictors of inappropriate DOAC dose administration. P values of less than 0.05 were considered statistically significant for all data analysis.

This study was conducted after receiving ethical approval from the Institutional Review Board of the hospital.

Results

A total of 337 patients were included in this study, of whom 194 (57.6%) received apixaban, 99 (29.4%) patients received rivaroxaban, and 44 (13.1%) were treated with dabigatran. Overall, the mean age of the study participants was 62.9±18.7 years. Male patients comprised 140 (41.7%) of the study population, while 196 (58.3%) were female. The median duration of follow-up was 9 months (range 1 to 14.3 months).

AF was the most frequent indication for prescribing DOACs in 226 (67.1%) of our patients, whereas VTE was the reason for anticoagulation in 114 (33.8%) patients. Hypertension was the most common co-morbidity in 56% of our cases, followed by diabetes mellitus in 46.6% of patients. The majority of our patients were not on anti-platelet therapy (260, 77.2%). The remainder received either acetylsalicylic acid, clopidogrel, or a combination of the two. The mean CHADS score at the time of initiating DOAC therapy was 1.8±1.6, while the mean HAS-BLED

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score was 1.75±1.5. The average creatinine clearance of our patients was 93.6±42.6 ml/minute (see Table 1).

Overall, 242 (71.8%) of patients were prescribed DOACs appropriately according to the FDA guidelines, whereas 95 patients (28.2%) received an inappropriate dose. Inappropriate low dose was identified in 74 (22%) patients, while 21 (6.2%) patients received an inappropriately high dose.

The starting dose of DOAC for apixaban and rivaroxaban was appropriately administered in 219/293 (74.7%) of patients. The starting dose was inappropriate in 74 (25.3%) patients: inappropriately low in 50 (17.1%) patients and inappropriately high in 24 (8.2%) patients. The maintenance dose of apixaban and rivaroxaban was appropriate in 248 (84.6%) patients. The maintenance dose was inappropriate in 45 (15.4%) patients: inappropriately low in 39 (13.3%) and inappropriately high in 6 (2%) patients (see Figures 1 and 2).

Overall, patients who received an inappropriate dose of DOAC had a significantly higher mean age ($p<0.001$), greater prevalence of diabetes mellitus ($p=0.034$), higher baseline CHADS score ($p=0.016$), and lower creatinine clearance ($p<0.001$) as compared to those who received an appropriate dose of DOAC. Table 2 compares the baseline characteristics of patients who received an appropriate dose of DOAC with those who received an inappropriate dose.

Multivariate logistic regression analysis identified age more than 75 years and creatinine clearance less than 50 ml/minute as significant predictors of a patient having received an inappropriate dose of DOAC ($p<0.05$). There was no association of DOAC dosing with gender, indication for anticoagulation, baseline HAS-BLED scores, or concomitant antiplatelet use. The complete results of the multivariate regression analysis are given below in Table 3.

Overall, 30 mortalities occurred during the study period. Occurrence of death was significantly associated with receiving an inappropriate dose of DOAC as compared to receiving an appropriate dose (15.8% *vs* 6.2%, $p=0.010$). There are no statistical differences in recurrent VTE, stroke, or bleeding between appropriate and inappropriate doses of DOAC. There is a trend toward a higher stroke rate in AF patients with inappropriate low dose and higher bleeding in patients with inappropriate high dose, but this was not statistically significant. Table 4 summarizes the complications seen in our study population, as well as their association with DOAC dosage.

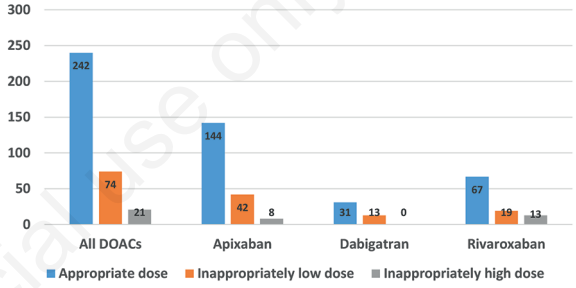

Figure 1. Overall analysis of direct-acting oral anticoagulants (DOACs) dosing regimens.

Table 1. Baseline characteristics.

	Total 337	Apixaban 194 (57.6%)	Dabigatran 44 (13%)	Rivaroxaban 99 (29.4%)
Age (years) mean±SD	62.9±18.7	63.8±18.1	70.5±14.9	57.7±19.5
Males N (%)	140 (41.5)	84 (43.2)	16 (36.4)	40 (40.4)
Weight (kg) mean±SD	79.3±20.7	78.1±19.3	82.5±18.8	80.2±23.8
Indication				
AF	223 (66.2)	138 (71.1)	40 (91)	45 (45.5)
VTE	114 (33.8)	56 (28.9)	4 (9)	54 (54.5)
Co-morbidities				
Diabetes mellitus	157 (46.6)	88 (45.3)	28 (63.6)	41 (41.4)
Hypertension	189 (56.1)	106 (54.6)	32 (72.7)	51 (51.5)
Heart failure	79 (23.4)	49 (25)	10 (22.7)	20 (20.2)
Ischemic stroke	56 (16.6)	37 (19)	7 (16)	12 (12.1)
Hemorrhagic stroke	20 (5.9)	18 (9.2)	2 (4.5)	0
CHADS score mean±SD	1.8±1.6	1.9±1.8	2.1±0.8	1.3±1.1
HAS-BLED score mean±SD	1.8±1.5	2.14±1.6	1.8±0.9	0.9±1.1
Creatinine clearance (ml/min) mean±SD	93.6±42.6	88.2±38.1	88.5±41.2	106.1±48.7
Concomitant anti-platelets				
Acetylsalicylic acid	57 (16.9)	39 (20)	4 (9.1)	14 (14.1)
Clopidogrel	12 (3.6)	12 (6.1)	0	0
Acetylsalicylic acid+Clopidogrel	7 (2.1)	4 (2)	1 (2.2)	2 (2)
None	260 (77.2)	138 (71.1)	39 (88.6)	83 (83.8)

AF, atrial fibrillation; VTE, venous thromboembolism.

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Discussion

This study assessed the burden and predictors of inappropriate prescribing practices of DOACs at a secondary care hospital in Riyadh. We found that almost one-third of patients received an inappropriate drug dose based on FDA guidelines. Previous studies have shown wide variation in the clinical practice of DOAC therapy, with inappropriate dose rates ranging from 8.4% to 32%.[22,23] These inappropriate dosing regimens include under-dosing, over-dosing, presence of any contraindication to drug prescription, and lack of dose adjustment for renal failure.[24] Inappropriate dosing in our patients was most frequently seen with the use of rivaroxaban as compared to other DOACs. Rivaroxaban and apixaban require higher doses at the time of acute thrombotic episodes with a reduced maintenance dose, while the dose of dabigatran remains consistent during therapy.

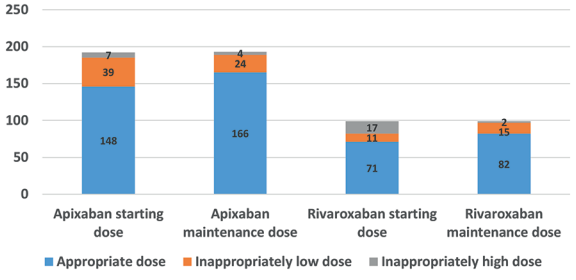

Figure 2. Appropriateness of dose adjustment of apixaban and rivaroxaban.

Prescription of an inappropriately low dose was the most encountered form of inappropriate dosing in our patients. This confirms the findings of previous similar studies, which also found under-dosing to be the most prevalent type of inappropriate dosing regimen.[25] A study by Sen *et al*. reported that physicians tend to prescribe lower doses of anticoagulants than recommended due to fear of life-threatening hemorrhagic complications.[26] This practice may be mitigated by adopting simpler drug regimens and the use of bleeding risk scores, such as the HAS-BLED score.

Our results showed that age of more than 75 years is a significant predictor of a patient having received an inappropriate dose of DOAC. This is similar to a study from Belgium that reported that DOACs tend to be inappropriately prescribed in patients aged more than 80 years.[27] The complexity of DOAC prescription increases with age due to wide variation in weight, renal function, co-morbidities, polypharmacy, and frailty. These findings highlight the need for a cautious approach to DOAC administration in older patients.

Furthermore, we found that a low creatinine clearance was also associated with a patient having received an inappropriate DOAC dose. Similarly, a study from Qatar found that poor renal function was a risk factor for incorrect DOAC dosage.[28] Both studies emphasized the need for physicians to be aware of accurate prescribing according to renal function status of individual patients. Standardized guidelines should be adhered to for this purpose.

We did not find any relationship between inappropriate

Table 2. Baseline characteristics of patients who received appropriate *vs* inappropriate doses of direct-acting oral anticoagulants (DOACs).

	Total 337	Appropriate dose 242 (71.8%)	Inappropriate dose 95 (28.2%)	p-value
Age (years) mean±SD	62.9±18.7	60.6±17.9	68.7±19.5	**<0.001**
Males N (%)	140 (41.5)	96 (39.6)	44 (46.3)	0.248
Weight (kg) mean±SD	79.3±20.7	80.5±21	76.5±19.7	0.258
Indication				
AF	223 (66.2)	160 (66.1)	63 (66.3)	0.990
VTE	114 (33.8)	82 (33.9)	32 (33.7)	0.279
Co-morbidities				
Diabetes mellitus	157 (46.6)	104 (43)	53 (55.8)	**0.034**
Hypertension	189 (56.1)	135 (55.8)	54 (56.8)	0.860
Heart failure	79 (23.4)	53 (22)	26 (27.3)	0.295
Ischemic stroke	56 (16.6)	32 (13.2)	24 (25.2)	0.008
Hemorrhagic stroke	20 (5.9)	14 (5.8)	6 (6.3)	0.273
CHADS score mean±SD	1.8±1.6	1.7±1.5	2.1±1.6	0.016
HAS-BLED score mean±SD	1.8±1.5	1.7±1.5	1.8±1.4	0.322
Creatinine clearance (ml/min) mean±SD	93.6±42.6	98.2±42.7	81.9±41.2	**<0.001**
Concomitant anti-platelets				
Acetylsalicylic acid	57 (16.9)	42 (17.4)	15 (15.8)	0.730
Clopidogrel	12 (3.6)	9 (3.7)	3 (3.2)	1.000
Acetylsalicylic acid+Clopidogrel	7 (2.1)	4 (1.7)	3 (3.2)	0.407

AF, atrial fibrillation; VTE, venous thromboembolism.

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Table 3. Multivariate logistic regression analysis of factors predicting inappropriate dose of direct-acting oral anticoagulants (DOACs).

	OR	95% CI	p-value
Age			
≥75 *vs* <75	2.76	1.67-4.56	**<0.001**
Gender			
Male *vs* female	1.32	0.82-2.13	0.260
CrCL			
≥50 *vs* <50	0.38	0.19-0.74	**0.005**
HAS-BLED			
≥3 *vs* <3	1.18	0.69-2.01	0.547
Concomitant anti-platelets			
Yes *vs* no	0.99	0.55-1.71	0.910
Anemia (hemoglobin <12)			
Yes *vs* no	1.61	0.96-2.71	0.070
Indication			
AF *vs* VTE	1.06	0.63-1.78	0.830

AF, atrial fibrillation; VTE, venous thromboembolism.

Table 4. Comparative analysis of direct-acting oral anticoagulants (DOACs) doses and clinical outcomes.

	Total 337	Appropriate dose 242 (71.8%)	Inappropriate dose 95 (28.2%)	p-value
VTE recurrence	4/114	3/82 (3.7%)	1/32 (3.1)	1.000
Stroke/embolism	13/223	7/160 (4.4%)	6/63 (9.5%)	0.201
Any bleeding	16	8/242 (3.3%)	8/95 (8.4%)	0.084
Major bleeding	7	4/242 (1.7%)	3/95 (3.2%)	0.408
Death	30	15/242 (6.2%)	15/95 (15.8%)	**0.010**

VTE, venous thromboembolism.

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DOAC dosing and gender or clinical indication for prescribing anticoagulation therapy. This is unlike the results of a previous study that found female gender to be a significant risk factor for inappropriate DOAC dosage.[29]

In our study, patients who received inappropriate doses of DOACs had a trend toward higher recurrent stroke and bleeding, but this was not statistically significant. Similarly, Sugrue *et al.* reported that AF patients who received inappropriate doses had non-significant differences in stroke and bleeding rates compared to AF patients who received appropriate doses.[29] In another study, a significantly higher rate of stroke was observed in AF patients treated with reduced apixaban dose.[14] The higher mortality rate observed in our study in patients with inappropriate doses could be explained by older patients, multiple co-morbidities, higher CHADS scores, and lower creatinine clearance in baseline characteristics of inappropriate dose compared to appropriate dose patients. The relatively small number of events and short follow-up duration could explain the non-significant outcome difference between inappropriate *vs* appropriate dose in our study.

Our study is limited due to its retrospective nature. Prospective multi-center studies are needed to further evaluate the prevalence and predictors of inappropriate DOAC dosing. Surveys should also be conducted among physicians of different specialties and varying degrees of seniority to assess where the gap in appropriate practice truly lies.

Conclusions

Approximately one-third of patients received an inappropriate dose of DOAC in our study population. The majority of these inappropriate doses comprised under-dosing and were encountered with the prescription of rivaroxaban and apixaban. Elderly age and low creatinine clearance were identified as significant predictors of inappropriate dosing in our patients.

References

1. Spahn G. Compliance with self-administration of heparin injections in outpatients. Eur J Trauma 2002;28: 104-9.
2. Lee A, Crowther M. Practical issues with vitamin K antagonists: elevated INRs, low time-in-therapeutic range, and warfarin failure. J Thromb Thrombolysis 2011;31:249-58.
3. Sikorska J, Uprichard J. Direct oral anticoagulants: a quick guide. Eur Cardiol Rev 2017;12:40.
4. Bauer KA. Pros and cons of new oral anticoagulants. Hematology Am Soc Hematol Educ Program 2013; 2013:464-70.
5. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.
6. Bertoletti L, Gusto G, Khachatryan A, et al. Effectiveness and safety of oral anticoagulants in the treatment of acute venous thromboembolism: a nationwide comparative cohort study in France. Thromb Haemost 2022;122: 1384-96.
7. Van Ganse E, Danchin N, Mahé I, et al. Comparative safety and effectiveness of oral anticoagulants in nonvalvular atrial fibrillation: the Naxos study. Stroke 2020;51:2066-75.
8. Chen A, Stecker E, Warden BA. Direct oral anticoagulant use: a practical guide to common clinical challenges. J Am Heart Assoc 2020;9:e017559.
9. Trujillo-Santos J, Di Micco P, Dentali F, et al. Real-life treatment of venous thromboembolism with direct oral anticoagulants: the influence of recommended dosing and regimens. Thromb Haemost 2017;117:382-9.
10. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace 2021;23:1612-76.
11. Martin KA, Beyer-Westendorf J, Davidson BL, et al. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. J Thromb Haemost 2021;19:1874-82.
12. Van der Horst SF, van Rein N, van Mens TE, et al. Inappropriate prescriptions of direct oral anticoagulants (DOACs) in hospitalized patients: A narrative review. Thromb Res 2023;231:135-140.
13. Ting C, Rhoten M, Dempsey J, et al. Evaluation of direct oral anticoagulant prescribing in patients with moderate to severe renal impairment. Clin Appl Thromb Hemost 2021;27:1076029620987900.
14. Yao X, Shah ND, Sangaralingham LR, et al. Non–vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. J Am Coll Cardiol 2017;69: 2779-90.
15. Camm AJ, Cools F, Virdone S, et al. Mortality in patients with atrial fibrillation receiving nonrecommended doses of direct oral anticoagulants. J Am Coll Cardiol 2020;76:1425-36.
16. Pradaxa® (dabigatran etexilate capsules) (2021) [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield. Available at: https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf
17. Eliquis® (apixaban) (2021) [package insert]. Bristol-Myers Squibb Company, Princeton. Available at: https://packageinserts.bms.com/pi/pi_eliquis.pdf
18. Xarelto® (rivaroxaban) (2016) [package insert]. Janssen Ortho, LLC, Gurabo. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202439s017lbl.pdf
19. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.
20. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093-100.
21. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16: 31-41.
22. Viprey M, Jeannin R, Piriou V, et al. Prevalence of drug-related problems associated with direct oral anticoagulants in hospitalized patients: a multicenter, cross-sectional study. J Clin Pharm Ther 2017;42:58-63.
23. Ruiz Ortiz M, Muñiz J, Raña Míguez P, et al. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: prevalence and associated factors. A subanalysis of the FANTASIIA Registry. Europace. 2018;20:1577-83.
24. Capiau A, De Backer T, Grymonprez M, et al. Appropriateness of direct oral anticoagulant dosing in patients with atrial fibrillation according to the drug labelling and the EHRA Practical Guide. Int J Cardiol 2021;328:97-103.
25. Sanghai S, Wong C, Wang Z, et al. Rates of potentially inappropriate dosing of direct-acting oral anticoagulants and associations with geriatric conditions among older patients with atrial fibrillation: the SAGE-AF study. J Am Heart Assoc 2020;9:e014108.
26. Sen S, Dahlberg KW. Physician's fear of anticoagulant therapy in nonvalvular atrial fibrillation. Am J Med Sci 2014;348:513-21.
27. Moudallel S, Steurbaut S, Cornu P, Dupont A. Appropriateness of DOAC prescribing before and during hospital admission and analysis of determinants for inappropriate prescribing. Front Pharmacol 2018; 9:1220.
28. Elewa H, El-Makaty H, Ali Z. Appropriateness of dabigatran and rivaroxaban prescribing in Qatar: a 5-year experience. J Cardiovasc Pharmacol Ther 2018;23: 155-61.
29. Sugrue A, Sanborn D, Amin M, et al. Inappropriate dosing of direct oral anticoagulants in patients with atrial fibrillation. Am J Cardiol 2021;144:52-9.

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