European Review for Medical and Pharmacological Sciences 2023; 27: 10076-10081

Utilization of direct oral anticoagulants in a Saudi tertiary hospital: a retrospective cohort study

H. SULTAN[1], M. ALNASSER[1], A. ASSIRI[1], F. TAWHARI[1], A. BAKKARI[2], M. MUSTAFA[1], W. ALOTAIBI[1], A. ASIRI[1], A. KHUDARI[1], A. ALSHREEM[1], M. AYOUB[1], S. ALKHATHAMI[1], H. BASNDWAH[1], O. ALSAEED[1], M. ALKREDEES[1], T. ALSALEM[1], A. ALHUWAIL[1], T. ALMALKI[1], Y. ALZAHRANI[1], F. ALSHAHRANI[1], B. ALQAHTANI[1], B. ALGHAMDI[1], A.R.N. IBRAHIM[3], M. ZAITOUN[1]

[1]Pharmaceutical Care Administration, Armed Forces Hospital Southern Region, Khamis Mushait Asir, Saudi Arabia
[2]College of Pharmacy, Jazan University, Jazan, Saudi Arabia
[3]Department of Clinical Pharmacy, College of Pharmacy, King Khalid University, Abha, Saudi Arabia

Abstract. – OBJECTIVE: This study aimed to assess the appropriateness of direct oral anticoagulants (DOACs) utilization in a Saudi tertiary hospital.

PATIENTS AND METHODS: Adult inpatients and outpatients diagnosed with atrial fibrillation, deep vein thrombosis, or pulmonary embolism were included in a retrospective cohort study. Patients received at least one month of apixaban, rivaroxaban, or dabigatran. The duration of the study at the Armed Forces Hospital Southern Region in Khamis Mushait, Saudi Arabia, was from January 1, 2019, to December 31, 2021. The study assessed the appropriateness of DOACs dosing, initial and follow-up monitoring, the presence of clinically significant interactions, and treatment duration adherence.

RESULTS: 778 patients were included in the analysis (mean age 71.34 ± 15.98 years, equal male and female representation). Rivaroxaban was administered to 40.8% of the patients, while apixaban and dabigatran were administered to 31.02% and 28.18% of the patients, respectively. The most prevalent indication for DOACs was atrial fibrillation (72.84%), followed by deep vein thrombosis and pulmonary embolism (27.16%). The most prevalent category of medication errors was inappropriate maintenance dose (41.7%), followed by inappropriate initial dose (37.97%) and lack of laboratory parameter monitoring (36.42%). 31.5 percent of the study sample lacked baseline renal functions, while 24.5% of patients lacked baseline liver functions. 115 patients (14.8%) had potential clinically significant interactions. Regarding treatment duration, 232 patients (29.8%) were improperly prescribed DOACs based on their indications.

CONCLUSIONS: In a significant proportion of DOAC patients, the prescribed rational DOAC utilization parameters were not implemented. The results of the study provide specific improvement areas and objectives for Anticoagulation stewardship programs.

Key Words:
Anticoagulants, DOACs, Medication errors.

Introduction

Anticoagulation stewardship is one of the recently introduced concepts and initiatives, defined as coordinated, efficient, and sustainable system-level initiatives designed to achieve optimal anticoagulant-related health outcomes and minimize avoidable adverse drug events. As direct oral anticoagulants (DOACs) are widely used in clinical practice, and to effectively implement anticoagulation stewardship, it is recommended to conduct a gap analysis to identify areas for improvement and assess opportunities for standardizing practices of DOACs.

Since DOACs introduction in clinical practice in 2010, they have dramatically changed the field of stroke and thrombosis prevention and management. DOACs are frequently preferred in clinical practice guidelines over other anticoagulants (injectable heparins and Vitamin K antagonists VKA) for their convenience of use, more predictable response, less individualized dosing, less

Corresponding Author: Hani A. Sultan, MD; e-mail: Ph-d.hanno@hotmail.com

frequent laboratory monitoring, fewer significant interactions, favorable safety profile, notably significantly lower incidence of bleeding.

Each DOAC has a different dosing schedule and dose modifications, mostly reductions, depending on one or more patient-specific factors, including age, weight, renal function, serum creatinine, indication, and concomitant medications[1-4]; the need to consider all of these parameters is associated with increased incidence of prescribing errors[5], For patients with renal and hepatic impairment, overdosing could increase the risk of drug accumulation and is associated with increased risk of bleeding[5]. Co-administration with medications that interfere with DOACs metabolism is associated with an increased risk of thrombotic events or bleeding episodes[6-8]. Thus, conducting studies involving these parameters and rational DOACs prescribing and monitoring assessment can provide specific objectives for the anticoagulation stewardship programs and ultimately improve DOACs patients' clinical outcomes.

As far as we know, this is the first study to evaluate DOACs utilization as a whole hospital experience in the Arab region, including the most significant parameters for DOAC utilization assessment.

Patients and Methods

Study Population and Design

After receiving approval from the institutional review board, a retrospective cohort study was conducted involving inpatients and outpatients of at least 18 years of age diagnosed with atrial fibrillation, deep venous thrombosis, or pulmonary embolism. Patients included in the analysis received at least one month of one or more direct oral anticoagulant agents, either apixaban, rivaroxaban, or dabigatran. The study duration was from January 1, 2019, to December 31, 2021, at the Armed Forces Hospital Southern Region in Khamis Mushait, Saudi Arabia. Patients were excluded from the analysis if they administered a DOAC for less than one month. For the year 2019, the hospital formulary included rivaroxaban and dabigatran. But from 2020 onward, dabigatran was replaced by apixaban based on the Pharmacy and Therapeutics Committee decision. The study was approved by the Research Ethics Committee of the Armed Forces Hospital Southern Region (AFHSRMREC/2022/PHARMACY/662). Informed consent has been waived by the research ethics committee due to the absence of patients' identifying data and the study design.

Data Collection

The initial list of patients on DOAC and data collection was done utilizing the hospital information system (HIS). Collected data included patient characteristics such as age, sex, body weight, clinical information such as indication, baseline and regular, relevant labs (including renal and hepatic function), estimated creatinine clearance (CrCl) using the Cockcroft and Gault formula, adherence to the recommended treatment duration, development of thrombotic events or bleeding episodes. Besides, prescription information was also recorded, including prescribed DOAC agent, initial and long-term dosage, frequency, presence of over or under-dosing, presence of concomitant drug interactions, particularly p-glycoprotein inhibitors, CYP450 3A4 inhibitor or inducer, or concomitant antiplatelet agent for more than the recommended duration.

Outcomes and Definitions

To meet the study objective, we calculated the proportions of patients with appropriate and inappropriate DOAC dosing compared to the FDA-approved dosing for general and special populations, adherence to the recommended initial and maintenance doses, commitment to the recommended laboratory monitoring, rate of the avoidable drug-drug interaction existence in the DOAC prescriptions, and adherence to recommended duration of therapy.

For the dosing appropriateness evaluation, underdosing was defined as a prescription dose that was reduced when the patient did not meet the criteria for dose reduction; while overdosing was defined as a prescription dose that was not reduced when the patient met the criteria for dose reduction or the total daily amount exceeds that recommended on the dosing guidelines. According to the International Society of Thrombosis and Hemostasis, significant bleeding was defined as bleeding that caused a fall in hemoglobin level of 2 g/dL or more. It is confirmed by the patient history of receiving bleeding management treatment such as tranexamic acid. In contrast, thrombotic events are defined by the patient history of receiving parenteral anticoagulant while avoiding the prescription of the oral anticoagulant that was administered before developing the thrombotic event.

Statistical Analysis

These collected data were analyzed using IBM SPSS 28 (IBM Corp., Armonk, NY, USA). Descriptive Statistics were used and presented as means ± SD for continuous variables and numbers and percentages for categorical variables. If inferential statistics is needed, the level of significance was predetermined to be $p < 0.05$.

Results

Upon extraction of data through the hospital information system, the patients who received DOACs as inpatients or outpatients during the study period were 1,050. Of these, 778 patients were included in the analysis, while 272 patients were excluded either due to incomplete data or not meeting the inclusion criteria. The patient's baseline characteristics are summarized in Table I.

Among the study sample, the most common category of medication errors encountered was inappropriate maintenance dose (41.7%) followed by inappropriate initial dose (37.97%), lack of laboratory parameters follow-up (36.42%), detailed about categories of dosing errors in the study sample are summarized in Table II. Regarding laboratory monitoring, in addition to the errors encountered in the follow-up clinics visits (36.4%), 31.5% of the study sample did not have baseline renal functions, while 191 patients (24.5%) did not have baseline hepatic functions. For drug interactions, concomitant administration of drugs significantly interacting with DOAC were prescribed in 115 patients (14.8%); these drug interactions included CYP 3A4 or P-gp inhibitors (e.g., clarithromycin, diltiazem, and verapamil), CYP 3A4 or P-gp inducers (e.g., carbamazepine) or dual antiplatelet therapy in addition DOAC. With regard to treatment duration, 232 patients (29.8%) were prescribed DOACs for inappropriate duration based on their indications.

Thirteen patients (1.6%) of the study sample developed thrombotic events, ten of them had received subtherapeutic doses of DOACs. Conversely, sixteen patients (2.05%) had major bleeding events, three of them only received supratherapeutic doses of DOACs.

Table I. Baseline characteristics of the study sample.

Variable	Result
Age (mean ± SD)	71.34 years ± 15.98
Weight (mean ± SD)	77.27 ± 16.03
Indication of DOAC	
Atrial fibrillation (number, %)	566, 72.84%
Venous thromboembolism (number, %)	211, 27.16%
Gender	
Male (number, %)	388, 49.94%
Female (number, %)	50.06%
DOAC administered	
Rivaroxaban (number, %)	317, 40.8%
Apixaban (number, %)	241, 31.02%
Dabigatran (number, %)	219, 28.19%

Table II. Categories of DOACs dosing errors.

Category of DOAC utilization error	Number and %
Inappropriate initial dose	295, 37.97%
Underdose	181, 61.36%
Overdose	107, 36.27%
Inappropriate frequency	215, 72.88%
Inappropriate maintenance dose	323, 41.7%
Underdose	193, 59.57%
Overdose	117, 36.1%
Inappropriate frequency	222, 68.52%

Discussion

In this single-center experience with the utilization of DOAC in AFIB and VTE patients across the inpatient and outpatient hospital settings, we tried to assess the adherence of prescribers with the recommended appropriate use of DOACs. The inappropriate DOAC dosing prevalence was reported as (37.9%) as initial doses, and (41.7%) as maintenance doses, the majority of patients received lower than the recommended doses (30.3%), and subtherapeutic doses were associated with an increased risk of cardiovascular hospitalization as reported by ORBIT-AF registry[9]. In contrast, those who received higher doses than recommended were (16.4%), with 15.8% of doses prescribed in inappropriate frequency. These inappropriate dosing findings are higher than the previously reported inappropriate DOAC dosing in atrial fibrillation patients (28.9%)[10] and venous thromboembolism patients [34% (19% for initial dose and 15% for maintenance doses)], respectively[11]. These reported inappropriate dosing might contribute to the reported bleeding episodes (4.5%) and thrombotic events (4.3%). Potential factors contributing to the reported high rate of inappropriate dosing and frequency include lack of

multidisciplinary teams' cooperation and focus on the antithrombotic rational use optimization across all hospital settings, in addition to the limited continuous education initiatives on the use of DOAC agents in a timely and updated manner for both physicians and pharmacists. This highlights the need for additional clinician and pharmacist education on the recommended DOAC dosing based on the patient's indication, hepatic, and renal functions.

Drug interaction is considered one of the challenges to the DOAC prescribers, in which P-glycoprotein and/or cytochrome P450 (CYP) 3A4 inhibitors or inducers may change the DOAC plasma concentration. In addition, the use of triple antithrombotic agents for more than the recommended duration or without regular patient assessment may significantly jeopardize patient clinical outcomes. These clinically significant interactions may increase the risk of bleeding episodes or thrombotic events according to the underlying mechanism of the interaction. Although there is an inconsistency between the DOAC plasma level and clinical outcomes, in which the adverse thrombotic events and bleeding episodes have been reported for patients with the "on therapy" range[12,13], there are cases in the literature[14] that have reported thrombotic events such as stroke, VTE, and intracardiac thrombus due to concomitant use of DOAC with enzyme inducer medications. Our findings show that 14.80% of DOAC patients were on concomitant interacting medications through the patient DOAC treatment course. This situation places the patients at risk of developing thrombotic and bleeding events and necessitates a thorough medication list review by pharmacists to ensure the absence of clinically significant DOAC drug interactions. Concerning DOAC monitoring, the irregular or lack of recommended DOAC laboratory monitoring may increase the incidence of serious adverse events, particularly bleeding events, as reported by Harper et al[15] in the context of AFIB patients. Within two months, 78 bleeding episodes occurred, with 12 of them being major bleeding events. Per Harper et al[15], these identified bleeding episodes were related to four contributing factors, including renal function impairment, a finding that highlights the importance of regular renal function test follow-up. Our findings showed that around one-third of patients did not measure the baseline renal and hepatic function test nor followed up regularly. Our results showed that about 30% of our study sample were not prescribed DOAC agents for the recommended therapeutic durations as per the approved medication labels and clinical practice guidelines. An irrational practice that can be associated with a risk of bleeding or thrombotic events development due to suboptimal or overuse of DOACs. One of the potential interventions to improve patient outcomes is an anticoagulation stewardship care model, in which the care model implementation reduced the incidence of significant bleeding or thrombotic events by -1.83% (-2.58%-1.08%) within two months, with the conclusion that anticoagulation stewardship initiative significantly reduced the composite endpoint of one or more bleeding episodes and one or more thrombotic events within three months after hospitalization[16]. One of the anticoagulation stewardship program elements is a pharmacist-led anticoagulant clinic that involves verifying the patient appropriateness for DOAC, patient education, and long-term monitoring of patients for adverse events in addition to follow-up their adherence to medications. This intervention reported that 93.6% of their patients received a correct dose[17].

One of the strengths of our study is the inclusion of the most recommended parameters to assess the appropriateness of DOAC utilization in the most clinically important indications, which are atrial fibrillation and venous thromboembolism in different hospital settings for hospitalized and ambulatory patients, to help other health institutions to assess their utilization of DOAC agents. Of note, recently published literature highlighted that DOACs are not only acting as anticoagulants in atrial fibrillation patients, but they also reduce inflammation and platelet reactivation[18]. Thus, DOACs could also be superior to vitamin K antagonists for stroke prevention in AF patients[19]. These findings add to the significance of the role of DOACs in this vulnerable population and provide more support to the rationale of our study.

This study is not limitation-free. First, the generalizability of the findings is limited by the single-center retrospective study design. One of the limitations is that many patients on DOACs are excluded due to incomplete data. This exclusion affects a significant percentage of patients. Third, we could not investigate the route cause for bleeding and thrombotic episodes of some patients due to incomplete data such as medications and care provided by other healthcare settings.

Conclusions

The data of this study provide a comprehensive overview of DOAC utilization in real-world clinical practice. Generally, in a significant percentage of DOAC patients, appropriate DOAC utilization parameters were not applied as recommended. As DOACs continue to be widely used in daily clinical practice, establishing an anticoagulation stewardship initiative and monitoring its implementation outcomes, seem necessary to improve DOAC utilization.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval

The study was approved by the research ethics committee of the Armed Forces Hospital Southern Region (AFHSRM-REC/2022/PHARMACY/662).

Informed Consent

Informed consent has been waived by the research ethics committee considering the study design and its outcomes that do not present any patients' identifying data.

Funding

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through a large group Research Project under grant number RGP2/145/44.

Availability of Data and Materials

As per the guidance of the institutional IRB, data should not be submitted to any third party without special permission from the IRB after masking all patients' identifiers.

Authors' Contribution

H. Sultan, and M. Zaitoun: contribution to research design, acquisition, analysis, and interpretation of data; drafted the manuscript; approved the submitted final version.
M AlNasser, A. Assiri, F. Tawhari, A. Bakkari, M. Mustafa, W. Alotaibi, A. Asiri, A. Khudari, A. Alshreem, M. Ayoub, S. Alkhathami, H. Basndwah, O. Alsaeed, M. Alkredees, T. Alsalem, A. Alhuwail, T. Almalki, Y. Alzahrani, F. Alshahrani, B. Alqahtani, B. Alghamdi, and A. R. N. Ibrahim: Contribution to research design, and acquisition of data; critically revised the manuscript; approved the submitted final version.

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