Journal of Cardiovascular Pharmacology and Therapeutics
2021, Vol. 26(6) 601-610

DOI: 10.1177/10742484211019657
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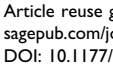

Prescribing Errors With Direct Oral Anticoagulants and Their Impact on the Risk of Bleeding in Patients With Atrial Fibrillation

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Abstract

Introduction: Anticoagulants are associated with significant harm when used in error, but there are limited data on potential harm of inappropriate treatment with direct oral anticoagulants (DOACs). We conducted a matched case-control study among atrial fibrillation (AF) patients admitting the hospital with a chronic treatment with DOACs, in order to assess factors associated with the risk of major bleeding. **Methods:** Patient data were documented using hospital's computerized provider order entry system. Patients identified with major bleeding were defined as cases and were matched with controls based on the duration of treatment with DOACs and number of chronic medications. Appropriateness of prescribing was assessed based on the relevant clinical guidelines. Conditional logistic regression was used to evaluate the potential impact of safety-relevant prescribing errors with DOACs on major bleeding. **Results:** A total number of 509 eligible admissions were detected during the study period, including 64 cases of major bleeding and 445 controls. The prevalence of prescribing errors with DOACs was 33%. Most prevalent prescribing errors with DOACs were "drug dose too low" (16%) and "non-recommended combination of drugs" (11%). Safety-relevant prescribing errors with DOACs were associated with major bleeding [adjusted odds ratio (aOR) 2.17, 95% confidence interval (CI) 1.14-4.12]. **Conclusion:** Prescribers should be aware of the potential negative impact of prescribing errors with DOACs and understand the importance of proper prescribing and regular follow-up.

Keywords

anticoagulants, direct oral anticoagulants (DOACs), prescribing errors, bleeding, safety

Introduction

A medication error is defined as "a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient."[1] Medication errors can occur at any stage of the treatment process, including prescribing, dispensing and administration. Prescribing errors (also referred to as a prescribing fault) include cases of inappropriate prescribing, ineffective prescribing, under-prescribing and overprescribing.[1] It has been suggested that among medication errors involving anticoagulants, prescribing errors cause the most harm.[2]

Anticoagulants are considered high-alert medications, defined as medications with a higher risk of causing significant harm when used in error.[3] Indeed, treatment with anticoagulants might lead to serious or fatal events, especially in cases of intracranial bleeding. Studies show that anticoagulants are one of the most common drug classes associated with preventable hospital admissions.[4,5] In addition, medication errors were identified as a common root cause in 40% of anticoagulation-related adverse events in a retrospective study.[6]

Direct oral anticoagulants (DOACs) are novel anticoagulants that were reported to be at least as effective as and safer than vitamin K antagonists (VKAs) for the prevention of stroke in phase III clinical trials in patients with non-valvular Atrial Fibrillation (nvAF).[7-9] In terms of safety, an important advantage of DOACs over VKAs was noted, as they were associated with similar rates of major bleeding and lower rates of intracranial bleeding, a rare but major cause of

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Manuscript submitted: July 20, 2020; **accepted:** April 21, 2021.

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disability and death, linked with nearly 50% mortality rate in patients treated with warfarin.[10]

These results, together with emerging real-world data, lead to a growing use of DOACs for prevention of stroke in atrial fibrillation (AF) (excluding patients with mechanical heart valve or moderate to severe mitral stenosis). In patients with AF who do not have mechanical heart valve or moderate to severe mitral stenosis, DOACs are considered as the first-line treatment according to both European and American guidelines for treatment of AF.[11,12]

All DOACs are given at a fixed dosing schedule and do not require routine coagulation panel (i.e., PT/INR) monitoring and monitoring of their concentration, as they have a more predictable pharmacodynamic and pharmacokinetic profile in relation to VKAs, with fewer drug interactions and rapid onset/offset of action.[13,14]

Despite their relative ease of use compared to VKAs, there are some considerations when choosing treatment with DOACs. As mentioned above, DOACs were evaluated in patients with nvAF, thus, patients with a mechanical prosthetic heart valve or moderate-to-severe mitral stenosis (mostly of rheumatic origin) are not eligible for treatment with DOACs.[7-9,15-17] In addition, periodical renal function monitoring is required in order to consider the need for dose adjustments (especially with dabigatran, as 80% of its dose is excreted through the kidneys). Thus, there are clear indications for dose reductions of DOACs, including creatinine clearance cut offs (together with age and body weight in case of apixaban).[11,15-17] Finally, although DOACs are considered to have much fewer drug interactions in comparison to VKAs, there are several pharmacokinetic interactions, mainly through effects on P-glycoprotein (P-gp) and/or Cytochrome P450 3A4 (CYP3A4) activities.[18,19] Besides the pharmacokinetic interactions, pharmacodynamic interactions are as relevant as with any other anticoagulant. Therefore, in case of a combination with anti-platelets or Non-Steroidal Anti Inflammatory Drugs (NSAIDs), a careful evaluation of the risk of bleeding against the potential benefit of treatments should be made.[18,20]

Missing information, infrequent monitoring, or lack of appropriate attention to the presence of valvular disease, renal function changes, and possible drug-drug interactions in the real-world setting might affect the safety profile of DOACs and potentially lead to negative outcomes, such as bleeding, as previously demonstrated with other anticoagulants. Limited data exist regarding such scenarios with DOACs, though there is growing evidence that prescribing errors with DOACs are not a rare phenomenon.[21-32]

We designed a case-control study among AF patients admitting to the hospital, in order to describe the types of prescribing errors with DOACs and to evaluate the association between prescribing errors with DOACs and the risk of major bleeding.

Methods

Study Design and Population

A matched case-control study was conducted in the Hadassah University Medical Center (Ein Kerem and Mt. Scopus) in Jerusalem from May 2015 to the end of January 2017. The study population was composed of AF patients who were admitted to the hospital with documentation of chronic treatment with DOACs prior to hospitalization and during their hospital stay. Patients with unknown treatment duration were excluded. The patients were identified through the hospital's computerized provider order entry system.

Cases and Controls

Cases were patients with bleeding, consistent with the International Society on Thrombosis and Haemostasis (ISTH) definition of bleeding, which includes transfusion of at least 2 units of blood or packed red cells, symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), fatal bleeding, or reduction in the hemoglobin concentration of more than 2 g/dL.[33] Bleeding could be diagnosed on admission or during hospitalization. Controls were patients who were admitted to the hospital and treated with a DOAC but did not have a major bleeding episode on admission and during hospitalization.

To avoid misclassification of hemoglobin drop during hospitalization due to conditions such as fluid shifts in hemodialysis, bone marrow failure and post-procedural bleeding as bleeding events, patients with no overt bleeding and with chronic kidney disease (estimated creatinine clearance [eCrCL] < 30 ml/min) who required hemodialysis on admission or during hospitalization, and patients with severe hematological disorder (e.g pancytopenia), or post-procedure, were classified as controls. Moreover, only cases with a decrease in hemoglobin levels to values of less than 12 g/dL were considered clinically relevant.

In patients admitted more than once because of a major bleeding during the study period, only the first hospitalization was counted as a case. Each case was matched with up to 25 controls, based on the duration of treatment with DOACs ($\pm$365 days) and number of chronic medications. All controls were reviewed for bleeding and found negative.

Data Collection

Data collected for each patient included demographics data, background conditions, medications consumed, reason for hospitalization and laboratory data. Detailed list of the collected data is provided in the supplemental material. Charlson Co-morbidity Index (CCI) was calculated for each patient according to his or her medical record at the time of admission.[34] Creatinine and hemoglobin levels were documented at baseline (defined as the average of the last 3 tests prior to DOACs treatment initiation) and at admission. Lab results were considered as "Baseline labs" only if they were obtained during the 3 months prior to initiation of treatment with DOACs In cases where no 3-month creatinine and hemoglobin tests were available, the last measurement before treatment initiation was used as the baseline. The eCrCL was calculated at baseline and at admission, using the Cockcroft-Gault (CG) method, as

Table 1. Characteristics of Study Population.[a]

	Cases (n = 64)	Controls (n = 445)	Overall (n = 509)	*P* Value
Age (years)	80.5 (76.0-86.0)	80.0 (72.0-85.0)	80.0 (74.0-86.0)	0.428
Female (%)	25 (39.1)	222 (49.9)	247 (48.5)	0.105
Weight category (%)				
<60 kg	10 (21.7)	53 (16.5)	63 (17.2)	0.103
60-100 kg	27 (58.7)	234 (72.9)	261 (71.1)	
>100 kg	9 (19.6)	34 (10.6)	43 (11.7)	
Type of DOAC (%)				
Dabigatran	8 (12.5)	63 (14.2)	71 (13.9)	0.002g
Rivaroxaban	20 (31.3)	63 (14.2)	83 (16.3)	
Apixaban	36 (56.3)	319 (71.7)	355 (69.7)	
Duration of treatment (days)	429 (120-677)	284 (120-534)	295 (120-549)	0.088
Number of chronic medications	8 (7.3-10.0)	9 (7-11)	9 (7.0-11.0)	0.458
CYP3A4/P-gp inhibitors (%)				
Any	24 (37.5)	130 (29.2)	154 (30.3)	0.177
Amiodarone	22 (34.4)	111 (24.9)	133 (26.1)	0.108
Dronedarone	0 (0.0)	1 (0.2)	1 (0.2)	>0.999
Verapamil	2 (3.1)	17 (3.8)	19 (3.7)	>0.999
Diltiazem	0 (0.0)	3 (0.7)	3 (0.6)	>0.999
Other[b]	0 (0.0)	2 (0.4)	2 (0.4)	>0.999
Other drugs (%)				
Antiplatelets[c]	17 (26.6)	95 (21.3)	112 (22.0)	0.346
NSAIDs	0 (0.0)	6 (1.3)	6 (1.2)	0.350
PPI	39 (60.9)	281 (63.3)	320 (63.0)	0.716
H2RA	1 (1.6)	14 (3.2)	15 (3.0)	0.482
Other[d]	17 (27.0)	101 (22.9)	118 (23.4)	0.468
Baseline eCLCr (ml/min)	63.4 (43.1-78.9)	55.9 (39.7-75.4)	56.4 (39.9-75.6)	0.182
eCLCr at admission (ml/min)	47.5 (33.6-67.2)	45.8 (31.2-64.8)	46.0 (31.5-65.6)	0.640
CHA2DS2 VASc score	5 (4-6)	5 (4-6)	5 (4-6)	0.877
HAS-BLED score	2 (1-3)	2 (1-3)	2 (1-3)	0.669
Prior bleeding (%)	6 (9.4)	76 (17.1)	82 (16.1)	0.117
Valvular heart disorders (%)				
Severe aortic stenosis[e]	1 (2.4)	20 (6.0)	21 (5.6)	0.332
s/p Mitral valve repair	1 (1.6)	5 (1.1)	6 (1.2)	0.761
s/p TAVI	0 (0.0)	16 (3.6)	16 (3.1)	0.123
Bioprosthetic heart valve	6 (9.4)	18 (4.0)	24 (4.7)	0.060
Other co-morbidities (%)				
Hypertension	58 (90.6)	384 (86.3)	442 (86.8)	0.338
Ischemic heart disease	32 (50.0)	174 (39.1)	206 (40.5)	0.097
Heart failure	35 (54.7)	270 (60.7)	305 (59.9)	0.361
Diabetes mellitus	29 (45.3)	203 (45.6)	232 (45.6)	0.963
Stroke/TIA	21 (32.8)	133 (29.9)	154 (30.3)	0.634
Advanced kidney disease[f]	13 (20.3)	104 (24)	117 (23.5)	0.520
Charlson co-morbidity index	3 (2-5)	3 (2-5)	3 (2-5)	0.757

[a] All continuous variables are expressed as medians (interquartile range).
[b] Tacrolimus, cyclosporine.
[c] Aspirin or P2Y12 inhibitors.
[d] SSRI/SNRI, corticosteroids.
[e] According to echocardiogram.
[f] (eCrCl < 30ml/min).
[g] Comparison of the frequency of different DOACs in the cases and the controls.

recommended in the European Heart Rhythm Association (EHRA) practical guide to the use of DOACs in AF patients.[18] When a patient's weight was unavailable, the Modification of Diet in Renal Disease (*MDRD*) formula was used.[35]

Each patient's risk of stroke was evaluated by CHA_2DS_2-VASc score, according to the information retrieved from the medical record at baseline.[36] The risk of bleeding was evaluated by HAS-BLED bleeding score, according to data retrieved from the medical record at admission.[37]

Prescribing Errors

Classification of prescribing errors with DOACs was derived from version 8 of the PCNE (Pharmaceutical Care

Table 2. A Detailed List of Prescribing Errors With DOACs Detected in All Study Patients and the Relevant Clinical Pharmacist Consultation (More Than One Error Is Possible in an Single Patient).

Type of prescribing error with DOACs (n = 168)	Pharmacist's recommendations	Details
Non-recommended drug (n = 18)	Switch to enoxaparin/warfarin	Treatment with Apixaban in eCrCl<15 ml/min or Dialysis—14 cases
	Consider a different DOAC or add a proton pump inhibitor	Treatment with Rivaroxaban in a patient with an increased risk of GI bleeding—2 cases
	Consider a different DOAC	Treatment with Dabigatran in a patient with an eCrCl of 31 ml/min—1 case
	Switch to enoxaparin/warfarin	Treatment with Rivaroxaban in eCrCl<15 ml/min—1 case
Contraindication (n = 4)	Consider a different DOAC	Treatment with Dabigatran in a patient with eCrCl < 30 ml/min—3 cases
	Switch DOAC	Treatment with Dronedarone in a patient on Dabigatran—1 case
Non-recommended combination of drugs (n = 55)	Stop Aspirin	DOAC + Aspirin with no indication—42 cases
	Stop Clopidogrel	DOAC + Clopidogrel with no indication—6 cases
	Stop dual antiplatelet therapy	DOAC + Aspirin + Clopidogrel with no indication – 2 cases
	Determine DOAC concentration, Coagulation specialist consultation	DOAC + Phenytoin/Carbamazepine (No TDM)—3 cases
	Determine DOAC concentration, Coagulation specialist consultation	Apixaban 2.5mg BID + Cyclosporin—1 case
	Adjust DOAC dose	Dabigatran 150 mg BID + Verapamil—1 case
Drug dose too low (n = 79)	Increase DOAC dose, Coagulation specialist consultation	Treatment with Apixaban 2.5mg BID with no 2 criteria for a reduced dose—54 cases
	Increase DOAC dose	Treatment with Rivaroxaban 15 mg OD in a patient with eCrCl>50 ml/min—4 cases
	Increase DOAC frequency	Apixaban once daily—13 cases Dabigatran once daily—8 cases
Drug dose too high (n = 11)	Adjust DOAC dose	Rivaroxaban 20 mg OD in eCrCl < 50 ml/min—7 cases Apixaban 5 mg BID in a patient with at least 2 criteria for dose reduction—3 cases Apixaban 10 mg OD—1 case
Other (n = 1)	Reintroduce treatment	An order to hold DOAC for 5 days after a procedure of endoscopic mucosal resection—1 case

Network Europe) classification scheme for drug-related problems.[38] A prescribing error with DOACs was detected when no accordance was found between the current treatment with DOACs and the recommended treatment, as defined in the relevant clinical guidelines.[11,18] Clinically relevant prescribing errors with DOACs included in this study were "non-recommended drug," "contraindication," "non-recommended combination of drugs," "drug dose too low," and "drug dose too high." All prescribing errors with DOACs were further categorized into safety-relevant or efficacy-relevant prescribing errors with DOACs, defined as prescribing errors which might increase the risk of bleeding or stroke, respectively. A detailed classification is presented in Supplementary Table 1. Treatment was considered to be contraindicated in cases of a general contraindication for DOACs (such as a rheumatic valvular disease or a mechanical heart valve) or a specific contraindication, such as dabigatran in a presence of severe renal impairment (eCrCL of less than 30 ml/min).[11,18] "Non-recommended combination of drugs" included anti-platelets (aspirin or P2Y12 inhibitors) in AF patients with ischemic heart disease that is stable for more than 1 year, according to guidelines.[39,40] This drug combination was considered recommended if a patients has recently (<1 year) undergoing percutaneous coronary intervention or acute coronary syndrome. "Non-recommended combination of drugs" included also P-gp/CYP3A4 inhibitors/inducers despite a clear recommendation for avoidance according to Summary of product characteristics (SmPC).[15-17] Dosage was considered to be inappropriately low or high when no accordance was found between the patient's dose and recommendations for dose adjustment, as described in Supplementary table 2.

Potential Confounders

Age and sex were defined a priori as potential confounders in the statistical analysis. Cases were matched with controls according to the follow-up time and the number of medications they were treated with. We did not match for age since the subjects were of the same age group [Median age was 80.5 years (IQR 76.0-86.0) for the cases and 80.0 years (IQR 72.0-85.0) for the controls]. Conditional logistic

Table 3. Number of Prescribing Errors With DOACs Among Cases and Controls (Patients With No Bleeding).[a]

	Cases (bleeding) (n = 64)	Controls (no bleeding) (n = 445)	Overall (n = 509)
Total number of prescribing errors	21 (32.8%)	147 (33.0%)	168 (33.0%)
Safety-relevant errors	16 (25.0%)	69 (15.5%)	85 (16.7%)
Efficacy-relevant errors	5 (7.8%)	78 (17.5%)	83 (16.3%)
Type of error			
Non-recommended drug	4 (6.2%)	14 (3.1%)	18 (3.5%)
Contraindication	1 (1.6%)	3 (0.7%)	4 (0.8%)
Drug dose too low	5 (7.8%)	74 (16.6%)	79 (15.5%)
Drug dose too high	2 (3.1%)	9 (2.0%)	11 (2.2%)
Non-recommended combination of drugs	9 (14.1%)	46 (10.3%)	55 (10.8%)
Other	0	1 (0.2%)	(0.2%)

[a] Percentages are calculated from number of cases and controls.

regression was used to match cases and controls. Since there was no statistical difference in age between the groups, and there is a considerable overlap between ages of both groups, regression model's adjustment was used to control for age. As for other risk factors, we matched for the number of medications, as an indirect measure for patients' comorbidities.

Additional covariates were included in the multivariate model if they had been associated with the outcome in the univariate analysis ($P < 0.1$). Potential variables designated for testing were: type of DOAC, hypertension, prior stroke, advanced kidney disease (eCrCl < 30 ml/min), anemia, prior bleeding, CCI, concomitant use of anti-platelets, CYP3A4/P-gp Inhibitors, NSAIDs, corticosteroids, Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Variables with a prevalence of less than 5% among the controls were not tested.

Statistical Analysis

Descriptive statistics were used in order to describe the study population and prescribing errors with DOACs. Percentages (%) were used to describe categorical variables. Continuous variables were described by using either mean with standard deviation (SD), for normally distributed variables, or median with interquartile range for variables with non-normal distribution. Chi-square test was used for comparison of nominal variables. Fisher exact test was used when sample sizes were small. Continuous variables were compared by student's t-test (in cases of a normal distribution) or the non-parametric Mann-Whitney test. Conditional logistic regression was used to calculate crude and adjusted odds ratio (OR) with 95% confidence interval (CI) in order to examine the association between prescribing errors with DOACs (including prescribing errors of any type, safety-relevant prescribing errors and total number of prescribing errors) and major bleeding as the primary outcome.

All statistical analyses were performed using IBM SPSS program, version 22. Results were considered significant at a P-value of less than 0.05 (2-tailed).

Ethics

The study was approved by the Helsinki Committee of Hadassah University Hospital (approval number 0365-15-HMO). Patients remained anonymous and no informed consent was required, due to the observational nature of the study.

Results

Study Population

During the study period, 64 patients were classified as bleeders, including 55 patients with bleeding on admission and 9 patients with bleeding during hospitalization. The 64 cases were successfully matched with 445 controls, thus 509 admissions were included in the final analysis. Characteristics of the patients included in the study are presented in Table 1.

The median age was 80 years and 48.5% were females. Median duration of treatment with DOACs was 295 days. Apixaban was the most commonly used DOAC, used in 69.7% of the admissions. There were no admission of patients treated with edoxaban, as this drug is not approved in Israel. Treatment with rivaroxaban was about twice more prevalent among cases as compared to controls (33.1% vs 14.2%), while treatment with apixaban was more prevalent among controls (71.7% vs 56.3%). These differences were statistically significant ($P < 0.001$). Apart from the differences described above, no other statistically significant differences were found between cases and controls.

Characterization of Prescribing Errors With DOACs

A total number of 168 prescribing errors with DOACs were identified. The vast majority of errors was originated from the community (Supplementary Table 3). A detailed list of prescribing errors with DOACs detected in the study is available in Table 2, including relevant clinical pharmacist intervention.

Most prevalent prescribing errors were "drug dose too low" (15.5%), followed by "non-recommended combination of drugs" (10.8%). The most common non-recommended drug combination was DOACs and aspirin, presenting in 42 of the 55 patients with non-recommended drug combination (76%).

Table 4. Association Between Safety-Relevant Prescribing Errors and the Use of Amiodarone With DOACs and Major Bleeding.

Variable		Crude OR (95%CI)	*P*-value	Adjusted OR[a] (95%CI)	*P*-value
Type of DOAC	Apixaban	1 (Ref)		1 (Ref)	
	Rivaroxaban	2.45 (1.16-5.15)	0.02	2.31 (1.07-5.01)	0.03
	Dabigatran	0.84 (0.27-2.57)	0.76	0.84 (0.27-2.87)	0.84
Concomitant use of Amiodarone		1.85 (0.95-3.61)	0.07	1.70 (0.87-3.32)	0.12
Safety-relevant prescribing errors with DOACs		2.17 (1.15-4.08)	0.02	2.17 (1.14-4.12)	0.02

Abbreviations: DOAC, direct oral anticoagulant; Ref, reference.
[a] Adjusted for age, sex, type of DOAC and concomitant use of amiodarone.

The number of the prescribing errors among cases and controls are presented in Table 3.

Among 509 patients included in the study (including cases and controls), 85 patients had safety-relevant prescribing errors, while 83 had efficacy-relevant prescribing errors. Among 85 patients with safety-relevant prescribing errors, most prevalent error was "non-recommended combination of drugs" (55), followed by "non-recommended drug" (18). The most common non-recommended drug combination was DOACs and aspirin, presenting in 42 of the 55 patients with "non-recommended drug combination."

Association Between Prescribing Errors With DOACs and Major Bleeding

Safety-relevant prescribing errors with DOACs were associated with an increased risk of major bleeding, compared to appropriate treatment or efficacy-relevant errors, after adjustment for potential confounders (adjusted OR 2.17, 95% CI 1.14-4.12). In addition, treatment with rivaroxaban was associated with an increased risk of major bleeding, compared to treatment with apixaban (adjusted OR 2.31, 95% CI 1.07-5.01). The results are summarized in Table 4. Apart from those, no other statistically significant association was found between various potential confounders and the outcome of interest, as summarized in Supplementary Table 4.

Association Between Non-Recommended Low DOACs Dose and Thromboembolic Complications

We performed an exploratory analysis in order to evaluate the relationship between non-recommended low dose and thromboembolic complications. We identified 10 cases of thromboembolic complications in the study population, 3 among the 75 patients who received non-recommended low dose, and 7 among the 434 patients without non-recommended low dose. The difference between groups was non-significant ($P = 0.171$, fisher exact test).

Discussion

We demonstrated that safety-relevant prescribing errors, including non-recommended combinations with drugs with DOACs, and treatment with rivaroxaban are associated with increased risk of major bleeding among AF patients admitting to the hospital.

Our second finding is regarding the patterns of non-recommended prescribing with DOACs among AF patients. Total prevalence of prescribing errors with DOACs has been reported to be highly variable, with a wide range of 2%-60%.[21-32] This can be explained by differences between populations studies, study methods and definitions of prescribing errors used in each study. The prevalence of prescribing errors with DOACs in our study was 33%, within the above-mentioned range.

Non-recommended low dose was the most prevalent prescribing error with DOACs in our study (16%). A similar prevalence was noted in another study from Israel, where DOAC underdosing was detected among 13% of hospitalized patients with AF.[41] A previous study has summarized the results of a review made by clinical pharmacists to DOAC orders among patients in our hospital. Nearly 30% of the consultations included recommendations for increasing the dose.[42] Additional studies outside of Israel have reported underdosing as the most common prescribing error with DOACs, with a prevalence ranging from 4% to 33%.[23,24,26,27,29-32] The phenomena of underdosing can be explained by prescribing physicians' concern of bleeding complications, especially intracranial bleeding. This has been suggested previously as a possible explanation for underuse of warfarin.[43]

A potential outcome of non-recommended low DOACs dose can include reduced efficacy of DOACs in AF and thromboembolic complications. However, if prescribing of lower than the recommended dose reflects patients' risk, patients' outcome may not necessarily be adversely affected. Indeed, association between non-recommended low DOACs dose and reduced efficacy of DOACs in AF has been observed in some of the previous studies,[44,45] but not in all.[46,47] In our exploratory analysis we did not observe a relationship between non-recommended low dose and thromboembolic complications. This may be related to the low rate of this outcome. A larger prospective study may be required to determine such association.

The second most prevalent prescribing error with DOACs in our study was non recommended combination of drugs (11%). Of these, 91% were combinations of DOACs with anti-platelets (50 of 55 cases).

There are limited data on the prevalence of non-recommended combinations of DOACs, especially regarding

combinations with antiplatelets. We have previously reported that alerts for potentially non recommended concomitant antiplatelet agents were mentioned in 20% of consultations made by clinical pharmacists regarding DOAC orders in our hospital.[42] It is highly important to evaluate the adequacy of antiplatelet therapy in patients treated with DOACs, as a subanalysis of the RE-LY trial has demonstrated an increased risk of major bleeding in patients treated with dabigatran and a single anti-platelet drug (HR 1.60, 95% CI 1.42-1.82). The risk has increased even more in patients with the combination of dabigatran with dual anti-platelet therapy (HR 2.31, 95% CI 1.79-2.98).[48] European Guideline for treatment of AF recommend avoiding these combinations in the absence of a clear indication, as the bleeding risk most probably outweighs the benefit in such situations.[11] Since we accessed each medical record manually, we had the ability to evaluate whether there was an indication for dual or triple antithrombotic therapy in patients receiving a combination of DOACs and antiplatelets in our study.

In addition to new information regarding patterns of inappropriate prescribing of DOACs among hospitalized patients, the main contribution of our study is the evaluation of the impact of safety-relevant prescribing errors (including non-recommended combinations of drugs) on major bleeding, an important clinical safety outcome in the AF population.

Only 2 studies have evaluated the association between prescribing errors with DOACs and clinical outcomes.[27,31] As observed in a large community-based cohort from the United States, underdosing of DOACs was associated with increased risk of cardiovascular hospitalization (HR 1.26, 95% CI 1.07-1.50). In addition, overdosing was associated with increased risk of all-cause mortality (HR 1.91, 95% CI 1.02-3.60). No association was demonstrated between overdosing and major bleeding, though a non-significant trend was noted (HR 1.71, 95% CI 0.91-3.24).[27] A smaller community-based retrospective study has demonstrated an association between the number of inappropriate criteria of treatment with DOACs, as evaluated by Medication Inappropriateness Index (MAI), and the risk of bleeding events (OR 1.9, 95% CI 1.2-3.2).[31] Two additional studies reported bleeding and thromboembolic events in patients with inappropriate prescribing of DOACs, but no quantitative assessment was performed.[21,24] Our study adds evidence on the potential association between prescribing errors with DOACs and negative clinical outcomes in the hospital setting, as safety-relevant prescribing errors with DOACs were associated with major bleeding (OR 2.10, 95% CI 1.15-3.82). To our knowledge, no other studies have addressed this question before in hospitalized patients.

When we tested the impact of potential risk factors on the risk of major bleeding in our study, the type of DOAC was found to contribute significantly, as rivaroxaban was associated with an increased risk of bleeding, compared to apixaban. A similar trend was noted when rivaroxaban was compared to dabigatran, although the difference was not statistically significant. This finding is consistent with previously published data, as rivaroxaban has been associated with an increased risk of bleeding outcomes in several real-world studies, when compared to other DOACs.[49-52]

The higher rivaroxaban use observed among cases may be related to a greater bleeding risk associated with the use of rivaroxaban, compared to apixaban or dabigatran in elderly population, as suggested in some previous studies.[51]

This difference was noted despite a higher HAS-BLED score among patients treated with apixaban as compared to rivaroxaban (2.28 vs 1.82, $P = 0.01$).This may be related to a high proportion of patients requiring dose reduction in our population, due to the larger magnitude of dose reduction with apixaban vs rivaroxaban (50% vs 25%), according to the guidelines for dose reduction with each of these DOACs. However, due to the retrospective design of our study we could not address this question directly.

The association between prescribing errors and negative clinical outcomes highlights the importance of awareness and alertness of clinical care providers to proper utilization of DOACs. Interventions including review and consultation by clinical pharmacists hematologists and clinical pharmacologists, and patient monitoring has been suggested as an effective method of ensuring adequate treatment with DOACs.[42]

Limitations and Strengths

Apart from its retrospective nature, our study has other several limitations.

Firstly, Neyman's bias, a type of selection bias that might occur in case-control studies, may be present.[53] Since our study population consisted of hospitalized patients, there might be an under-representation of fatal bleeding events occurring at home or on the way to the hospital, weakening the association between prescribing errors and major bleeding.

Secondly, since the data was collected from the hospital's computerized records, some of the information could be lacking or inaccurate, as no contact was made with the patients or their doctors. As a result, the definition of major bleeding in many cases was based on a hemoglobin decline and no information was available on clinical bleeding in many of these cases.

In order to overcome this gap, we applied a number of inclusion criteria to define major bleeding. These criteria were used to avoid misclassification of hemoglobin drop due to conditions such as hematological disease or chronic renal failure as major bleeding. It should be noted that the data for each patient was collected manually, in order to minimize the possibility of inaccuracies. The chronic medication list in the medical record was verified by access to each patient's dispensing records, and each diagnosis code was verified by reviewing the patient's medical record thoroughly. By this, we tried to minimized possible information inaccuracies.

Thirdly, there were differences in the use of DOACs in our population. Most patients were treated with apixaban (70%) while less patients took dabigatran (14%) and rivaroxaban (16%). Unequal distribution may indicate trends in the choice of a specific DOACs for a specific patient (for example: an

older patient will receive apixaban) and thus affect the risk of bleeding.

The characteristics of hospitalized patients are different from the community population inpatients tend to be older, with more background diseases (such as kidney failure, various medications) that affect the risk of bleeding. As a result, it is difficult to generalize our finding to community patients.

Nevertheless, the study adds real-world data regarding treatment with DOACs in complex patient population and highlights the importance of proper prescribing in such patients. Finally, as could be expected, the evaluation of the potential association between prescribing errors with DOACs and efficacy outcome (the risk of stroke) was not possible, as the number of stroke events was much lower than major bleeding events in our study.

Our study demonstrates some of the pitfalls in DOACs treatment. Although DOACs do not require INR monitoring as VKAs do, they do require monitoring and follow up to ensure prescribing is appropriate (and no contraindication to treatment exists), dosing is appropriate (according to age, weight and renal function, all require periodic follow-up), and no significant drug-drug interactions exist. Periodical laboratory tests can identify factors increasing bleeding risk (such as thrombocytopenia) or suggesting occult bleeding (such as a decline in hemoglobin). Follow up should also ensure that patients are able to obtain DOACs and take them as prescribed, and that accessibility to treatment is un-interfered.

Conclusion

Prescribing errors with DOACs occur in nearly a third of the AF patients who were admitted the Hadassah hospital, mostly in forms of non-recommended low dose or non-recommended combinations with other medications. Safety-relevant prescribing errors with DOACs, including non-recommended combinations, non-recommended high dose and selection of DOAC, were associated with an increased risk of major bleeding in these patients. Prescribers should be aware of the potential negative impact of prescribing errors with DOACs and understand the importance of proper prescribing and regular follow-up.

Authors' Note

The data underlying this article will be shared on reasonable request to the corresponding author.

Author Contributions

Bruria Hirsh Raccah and Yevgeni Erlichman contributed equally and should be considered as first authors. Ilan Matok and Mordechai Muszkat contributed equally to this work and jointly directed it.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Muszkat reports grants from Pfizer Global Medical Grants, outside the submitted work.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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