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Original Research

Real-world study of direct oral anticoagulant dosing patterns in patients with atrial fibrillation

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Abstract

Background: Direct oral anticoagulants (DOACs) are preferred for stroke prevention in atrial fibrillation (AF). However, off-label doses have been associated with increased risk of adverse events.

Objective: The objective of this study was to compare the frequency and outcomes of labeled versus off-label DOAC dosing in patients with AF.

Methods: This retrospective cohort study included adults diagnosed with nonvalvular AF (NVAF), discharged from University of Utah Health on DOAC therapy between 7/1/2017 and 9/30/2017. The primary outcome was off-label DOAC dosing frequency, defined as dosing inconsistent with manufacturer labeling. Secondary outcomes included variables associated with off-label dosing and a composite of adverse events (major bleeding, thromboembolism, and all-cause mortality) in the 90 days following the index hospital discharge.

Results: Of 249 included patients, 16.1% were discharged with off-label dosing. Factors associated with off-label dosing included advanced age, lower body mass index, decreased renal function, use of rivaroxaban, and hepatic impairment. The majority of off-label patients (70%) received lower-than-recommended DOAC dosing. Prescriber rationale for off-label prescribing was documented in 25% of patients and included anti-Xa guided dosing, high risk for bleeding or thromboembolism, and prior history of on-therapy adverse events. The rate of adverse events between labeled and off-label DOAC doses was not statistically different (10.0% vs. 6.7%, p=0.299), although this is likely due to small sample size.

Conclusions: Off-label DOAC prescribing for stroke prevention in NVAF at University of Utah Health was consistent or lower than previously published studies. Off-label dosing most often involved under-dosing of rivaroxaban. Future research should investigate the role of provider rationale and insight in optimizing DOAC therapy outcomes.

Keywords

Anticoagulants; Thromboembolism; Atrial Fibrillation; Stroke; Off-Label Use; Drug-Related Side Effects and Adverse Reactions; Patient Outcome Assessment; Retrospective Studies; United States

INTRODUCTION

Direct oral anticoagulants (DOACs) are now recommended as the treatment of choice for most patients with atrial fibrillation (AF).[1-4] DOACs do not require international normalized ratio monitoring or frequent dose adjustments like warfarin, and have fewer drug and dietary interactions. However, approved prescribing information indicates that DOAC doses should be individualized based on weight, renal function, age, and concomitant medications.[1,5-7] Previous studies have examined prescribing patterns and off-label DOAC dosing in various settings.[1,8-12] Off-label dosing is defined as any dose that is inconsistent with approved prescribing information. Overall, these studies have shown a wide variety of off-label prescribing patterns with rates ranging from 14.0% to 57.7%.[1,8-13] Some studies have documented an association between off-label DOAC dosing and increased risk of adverse events but others have not. Although prescribers may have valid reasons for using off-label DOAC doses, it is important to note that no studies have demonstrated an association between this practice and improved anticoagulation therapy outcomes. It is therefore important for healthcare systems to monitor DOAC prescribing practices and identify any related patient safety issues. Therefore, the purposes of this study were to assess the rate of off-label DOAC dosing at University of Utah Health, identify provider rationale for off-label dosing, and analyze the potential association between off-label DOAC dosing and anticoagulation-related adverse events.

METHODS

This was a retrospective study conducted at University of Utah Health. Queries of electronic medical records identified adult patients (over 18 years old) with a new or existing diagnosis of nonvalvular AF (NVAF) who were discharged from University of Utah Health with a DOAC prescription between July 1, 2017 and September 30, 2017. Patients with prosthetic heart valves or any indication for anticoagulation other than NVAF were excluded. Patient demographic data, comorbidities, renal function (creatinine clearance), DOAC type and dosage, and prescriber rationale for dose selection, were collected via manual chart review. Diagnosis of NVAF was also verified during chart review. Creatinine clearance was calculated via the Cockcroft-Gault equation using total body weight (TBW) or adjusted body

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weight (ABW) if TBW was more than 25% greater than ideal body weight (IBW). Investigators also documented whether the patient was enrolled in the University of Utah Health Thrombosis Service. Study data were collected and managed using REDCap electronic data capture tools.[14,15] Patients were assigned to one of two groups, defined by the DOAC dose at hospital discharge: "labeled" or "off-label" (consistent or inconsistent with United States Food and Drug Administration-approved prescribing information, respectively). Patients with off-label DOAC dosing were further categorized as having higher- or lower-than-recommended dosing. Each chart was reviewed by two investigators. Discrepancies regarding NVAF diagnosis, DOAC dosing classification, and adverse events were adjudicated by a third investigator.

The primary outcome was the proportion of patients receiving labeled vs. off-label DOAC doses. Secondary outcomes included (1) identification of variables associated with off-label dosing, (2) a composite adverse event rate consisting of: thromboembolism; major bleed or clinically relevant nonmajor bleed (CRNMB); or death from any cause. Major bleeding and CRNMB were defined using criteria established by the International Society of Thrombosis and Haemostasis.[16] Patients were followed for 90 days after hospital discharge documenting any

Table 1. Patient Characteristics of atrial fibrillation patients prescribed a direct oral anticoagulant

Patient characteristics	Total (n=249)	Labeled (n=209)	Off-label (n=40)	p-value
Mean Age in years (SD)	72.0 (SD 11.8)	71.2 (SD 11.9)	76.6 (SD 10.7)	**0.006**
< 65 years, n (%)	54 (21.7)	51 (24.4)	3 (7.5)	0.75
65-79 years, n (%)	128 (51.4)	109 (52.2)	19 (47.5)	0.75
≥80 years, n (%)	67 (26.9)	49 (23.4)	18 (45.0)	0.65
Male sex, n (%)	154 (61.8)	127 (60.8)	27 (67.5)	0.42
Race				0.49
Caucasian, n (%)	237 (95.2)	197 (94.3)	40 (100.0)	0.12
Black or African American, n (%)	3 (1.2)	3 (1.4)	0	1.00
Asian, n (%)	1 (0.4)	1 (0.5)	0	1.00
Other/Not reported, n (%)	8 (3.2)	8 (3.8)	0	0.362
Mean Weight in kg (SD)	89.0 (SD 23.5)	90.1 (SD 25.1)	83.1 (SD 17.4)	**0.03**
<60 kg, n (%)	18 (7.2)	17 (8.1)	1 (2.5)	0.32
60-120 kg, n (%)	208 (83.5)	170 (81.3)	38 (95.0)	**0.03**
>120 kg, n (%)	21 (8.4)	20 (9.5	1 (2.5)	0.214
Unreported, n (%)	2 (0.8)	2 (0.9)	0	1.00
Mean BMI in kg/m^2 (SD)	29.5 (SD 7.0)	30.0 (SD 7.5)	27.3 (SD 5.0)	**0.006**
<18.5, n (%)	6 (2.4)	6 (2.9)	0	0.59
18.5 to <25, n (%)	69 (27.7)	55 (26.3)	14 (35.0)	0.26
25 to <30, n (%)	69 (27.7)	53 (25.4)	16 (40.0)	0.06
30 to <35, n (%)	52 (20.9)	44 (21.1)	8 (20.0)	0.88
35 to <40, n (%)	30 (12.0)	29 (13.9)	1 (2.5)	0.06
>40, n (%)	21 (8.4)	20 (9.5)	1 (2.5)	0.21
Unable to calculate due to missing data, n (%)	2 (0.8)	2 (0.9)	0	1.00
Mean CrCl (mL/min) (SD)	70.3 (SD 31.6)	72.2 (SD 32.0)	60.4 (SD 30.6)	**0.03**
<15, n	0	0	0	n/a
15-29, n (%)	10 (4.0)	7 (3.3)	3 (7.5)	0.22
30-49, n (%)	57 (22.9)	41 (19.6)	16 (5.0)	0.005
50-79, n (%)	107 (43.0)	95 (45.5)	12 (30.0)	0.07
≥80, n (%)	65 (26.1)	58 (27.8)	7 (17.5)	0.18
Unable to calculate due to missing data, n (%)	10 (4.0)	8 (3.8)	2 (5.0)	0.73
Mean Serum Creatinine (g/dL) (SD)	1.1 (SD 0.3)	1.0 (SD 0.3)	1.2 (SD 0.6)	0.06
Mean CHA_2DS_2-VASc Score (SD)	3.3 (SD 1.7)	3.2 (SD 1.6)	3.9 (SD 1.8)	0.23
0-1, n (%)	31 (12.4)	29 (13.9)	2 (5.0)	0.19
2-3, n (%)	111 (44.6)	95 (45.5)	16 (40.0)	0.67
4-6, n (%)	96 (38.6)	78 (37.3)	18 (45.0)	0.38
≥7, n (%)	11 (4.4)	7 (3.3)	4 (10.0)	0.08
Mean Number of Interacting medications at baseline	0.5 (SD 0.7)	0.4 (SD 0.6)	0.7 (SD 0.8)	**0.005**
Low-dose daily aspirin, n (%)	56 (22.5)	44 (21.1)	12 (30.0)	0.21
P2Y12 inhibitors, n (%)	9 (3.6)	4 (1.9)	5 (12.5)	**0.007**
NSAIDs, n (%)	23 (9.2)	19 (9.1)	4 (10.0)	0.77
Other*, n (%)	15 (6.0)	9 (4.3)	6 (15.0)	**0.009**
Referred to Thrombosis Service, n (%)	24 (9.6)	21 (10.0)	3 (7.5)	0.62
Child-Pugh Class				
A, n (%)	3 (1.2)	2 (1.0)	1 (2.5)	0.41
B, n (%)	6 (2.4)	2 (1.0)	4 (10.0)	**0.007**
DOAC Prescribed				
Apixaban, n (%)	155 (62.2)	138 (66.0)	17 (42.5)	**0.005**
Dabigatran, n (%)	10 (4.0)	6 (2.9)	4 (10.0)	**0.04**
Rivaroxaban, n (%)	84 (33.7)	65 (31.1)	19 (47.5)	**0.04**

Bolded p-values indicate statistical significance.
*Modifiers of p-glycoprotein and/or CYP3A4
BMI: body mass index, CrCl: creatinine clearance, DOAC: direct oral anticoagulant, n/a: not applicable, NSAID: non-steroidal anti-inflammatory drug, SD: standard deviation

Table 2. Off-Label Direct Oral Anticoagulant Dosing

	Total n (%)	Higher-than-recommended Dosing n (%)	Lower-than-recommended Dosing n (%)	Other* n (%)
All DOACs	40 (16.1)	7 (17.5)	28 (70.0)	5 (12.5)
Dabigatran	4	0	4 (10)	0
Rivaroxaban	19	5 (26.3)	12 (63.2)	2 (10.5)
Apixaban	17	2 (11.8)	12 (70.6)	3 (17.6)

*Reasons dosing classification was prevented in these patients included concomitant St. John's wort (n=1) and phenytoin (n=1) which are contraindicated with apixaban; and Child-Pugh B or C hepatic impairment where no dosing guidance is provided (n=3). DOAC: direct oral anticoagulant

occurrence of the individual components of the composite outcome.

Categorical variables were summarized using percentages, and continuous variables as mean (standard deviation [SD]). Differences between the labeled and off-label groups were compared using the chi-squared test of association or Fisher's exact test for categorical variables or student's t-test for continuous variables. P-values <0.05 were considered statistically significant.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Utah Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due to the retrospective chart review design of the study, the University of Utah Institutional Review Board waived the requirement for informed consent.

RESULTS

Between July 1, 2017 and September 30, 2017, a total of 275 patients with NVAF were identified as receiving DOAC prescriptions at discharge. Twenty-six patients (9.5%) were excluded due to missing or incomplete data that prevented investigators from classifying them as receiving labeled or off-label DOAC dosing, leaving 249 patients for analysis. The mean age of included patients was 72 years (SD 11.8), most patients were male (61.8%) and Caucasian (95.2%) (Table 1). Apixaban was the most frequently prescribed DOAC (62.2%), followed by rivaroxaban (33.7%) and dabigatran (4%). No patients were prescribed edoxaban. Aspirin and non-steroidal anti-inflammatory drugs were prescribed in 22.5% and 9.2% of patients, respectively. Concomitant use of CYP3A4 and/or p-glycoprotein modifiers was infrequent (3.6%).

Overall, 40 patients (16.1%) were prescribed off-label DOAC doses. Compared to the group who received labeled dosing, the off-label DOAC group had a higher mean age (71.2 vs. 76.6 years, p=0.006), lower mean body mass index (BMI) (30.0 vs. 27.3 kg/m2, p=0.006), lower mean creatinine clearance (CrCl) (72.2 vs. 60.4 mL/min, p=0.03), and more interacting medications at baseline (mean 0.4 vs. 0.7, p=0.005). Patients in the off-label group were most likely to be prescribed rivaroxaban (47.5% vs. 31.1% in the labeled group, p=0.044), then apixaban (42.5% vs. 66.0%, p=0.005), followed by dabigatran (10% vs. 2.9%, p=0.035). Patients with Child-Pugh Class B liver disease were also more likely to be prescribed off-label DOAC doses (10.0% vs. 1.0%, p=0.007).

Most off-label doses were lower-than-recommended (70.0%) (Table 2). Higher-than-recommended doses occurred in 17.5%, and the DOAC dose could not be classified in 5 patients (12.5%) due to the presence of a contraindicated drug-drug interaction or Child-Pugh B or C hepatic impairment. Prescriber rationale for off-label dosing was documented for only 25.0% of patients and included the use of anti-Xa guided DOAC dosing, reducing apixaban dose based on only one of three criteria specified in the product labeling for lowering the dose, occurrence of an adverse event while on another DOAC, fluctuating or impaired renal function, and high CHA2DS2-VASc score.

A total of 18 composite adverse events occurred in the 90 days following hospital discharge, 14 in the labeled dosing group (6.7%), and 4 in the off-label group (10.0%, p=0.299) (Table 3). Of these, 11 were deaths including all 4 of the events in the off-label group. Only 2 deaths, one in each group, had documentation suggesting bleeding complications contributed to the death along with other factors and none indicated thromboembolic causes. This off-label patient was receiving a low dose. A total of 5 bleeding events occurred, all of which were in the labeled dosing group. Only 1 (a GI bleed) was a major bleed. The 4 CRNMBs were surgical site, genitourinary, ear, and one patient with both hemoptysis and melena.

DISCUSSION

This study found a rate of off-label DOAC dosing for NVAF at University of Utah Health of 16.1%, which was similar to or lower than has been reported in other studies.[8-10,13] A study using similar methodology but with a VTE population was also conducted by the authors at the same institution.[10] Although DOAC dosing criteria are different between NVAF and VTE creating different potential for inappropriate dosing patterns, a similar rate of 15.9% was

Table 3. Adverse Outcomes in Patients Taking Direct Oral Anticoagulants

	Total (n=249) n (%)	Labeled (n=209) n (%)	Off-Label (n=40) n (%)	p-value
Composite: (bleeding*, thromboembolism, all-cause mortality)	18 (7.2)	14 (6.7)	4 (10.0)	0.50
Bleeding*	5 (2.0)	5 (2.4)	0	1.00
Thromboembolism	2 (0.8)	2 (1.0)	0	1.00
All-cause mortality	11 (4.4)	7 (3.3)	4 (10.0)	0.08

*Major bleeding or clinically relevant non-major bleeding using ISTH definitions

found. Patients in this study were more likely to receive a lower than recommended dose if they were older, had lower CrCl, and had a lower BMI, although the differences are not likely clinically significant. Some prior studies have reported more off-label dosing with apixaban due to a more complex dose reduction scheme, where a patient must meet 2 of 3 clinical criteria to be eligible for dose reduction.[5,8] In contrast, our study showed more off-label dosing with rivaroxaban, most commonly lower-than-recommended dosing based on renal function. The approved prescribing information recommends a dose reduction from 20 mg daily to 15 mg daily for atrial fibrillation patients with a CrCl of less than 50 mL/min. Patients receiving the lower-than-recommended rivaroxaban dose in our study were receiving the 15 mg daily dose despite having CrCl >50 mL/min. This may have been due to fluctuating renal function or providers being unaware of the CrCl threshold for dose adjustment. Age, weight and CrCl seemed to be predictive of off-label dosing in general, similar to a report by Gibson *et al*.[11] Although the mean number of interacting drugs was higher statistically higher in patients receiving off-label dosing, the clinical relevance of this observation is questionable.

While we found similar rates of off-label dosing to other studies, the adverse event rate in this study was lower than reported by others (10.0% vs. 23.7%).[1,8-13] Much of the provider rationale given for off-label DOAC dosing seemed to be related to fluctuating renal function, anti-Xa-guided DOAC dosing, and prior history of adverse events. It is possible that the rationale for off-label dosing was, in fact, clinically appropriate. However, only 1 in 4 providers documented their reasoning for deviating from approved prescribing information. This finding highlights a potential improvement opportunity as it would seem prudent from a medical-legal perspective to clearly document the rationale for deviating from approved labeling in the patient's medical record. At minimum, institutions should routinely assess DOAC prescribing and adverse events to identify potential areas for improvement. Reinforcing labeled dosing at initial prescribing and as well as evaluating criteria for dose adjustment such as age, weight, and renal function for subsequent prescriptions may optimize outcomes in DOAC patients. Anticoagulation monitoring services could be better utilized to ensure appropriate DOAC prescribing. In this study, less than 10% of patients were referred to and received follow-up from the Thrombosis Service, and due to the small sample size, there was no statistical difference in off-label prescribing between those referred and not referred to the service. Currently, referral to the service and pharmacist review of DOAC prescribing is optional. Subsequent to this study, the electronic medical record now includes dosing guidance upon ordering of a DOAC. Finally, closer follow-up for adverse events in patients using off-label DOAC dosing with provider rationale may be warranted. The proportion of patients in our study experiencing the composite outcome was numerically higher in the off-label group, but this difference was not statistically significant. All-cause mortality was also 3-fold higher in the off-label group, a finding that is potentially concerning and requires additional study. Our study was not adequately powered to detect differences in clinical outcomes.

There are limitations to this study. First, this was a single-center study with mostly Caucasian patients, therefore the results may not be generalizable to other populations. However, the intention of this analysis was to determine how University of Utah Health compared to DOAC prescribing patterns reported in the literature. Second, the limited follow-up time of three months may not have been adequate time to observe and obtain an accurate adverse event rate or patients may have presented to an outside hospital with an adverse event that was not captured. Third, patients in the study could have been at any stage of their DOAC therapy and were not necessarily new starts after the index hospitalization. However, we believe the risk estimates reported in our study reflect those associated with efforts to screen for off-label DOAC dosing during the hospital discharge process. Fourth, we analyzed DOACs as a class but recognize that characteristics of individual DOACs tied to approved labeling such as CrCl and BMI may have factored into off-label dosing decisions. Lastly, this study is subject to the biases associated with retrospective studies.

Future studies may benefit from looking at a larger cohort, with a longer duration of follow-up. Provider rationale for off-label DOAC dosing as it relates to adverse events requires additional exploration. It also may be reasonable to compare labeled and off-label dosing in patients newly started on DOAC therapy and with those who have been stable on DOAC therapy to determine if patients prescribed off-label doses are more likely to have adverse events at a certain time point in their therapy. Finally, future studies should aim to identify interventions which could reduce overall off-label prescribing as this may help reduce adverse event rates.

CONCLUSIONS

The off-label DOAC prescribing rate at University of Utah Health was consistent with other studies reported in the literature. Off-label DOAC doses were primarily lower-than-recommended in the approved prescribing information and occurred more commonly in patients on rivaroxaban, older patients, those with lower BMI, lower creatinine clearance, and those receiving interacting drugs. Adverse events were not significantly different between labeled and off-label DOAC dosing groups. Future research should investigate the role of provider rationale and insight in optimizing DOAC therapy outcomes.

CONFLICT OF INTEREST

Whitney L. Gustafson, John A. Saunders and Aubrey E. Jones declare that they has no conflict of interest. Sara R. Vazquez declares that she is an editorial consult for UpToDate® and a member of the Anticoagulation Forum Board of Directors. Daniel M. Witt declares that he is a member of the Anticoagulation Forum Advisory Council and has received grant funding unrelated to this study from Roche Diagnostics Corporation (RD003737)..

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