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RESEARCH LETTER

Correcting Inappropriate Prescribing of Direct Oral Anticoagulants: A Population Health Approach

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Direct oral anticoagulant (DOAC) use has expanded rapidly in the past decade for stroke prevention in atrial fibrillation and treatment of venous thromboembolism. However, they are frequently prescribed off label with associated increased risk of hospitalization, bleeding, stroke, and death.[1–3] Given the frequency of off-label use and overall growth in DOAC prescribing, methods to improve appropriateness of DOAC prescribing are needed.

Patients newly starting DOAC medications at 1 of 3 academic health systems participating in the Blue Cross Blue Shield of Michigan-sponsored MAQI[2] (Michigan Anticoagulation Quality Improvement Initiative) collaborative were randomly enrolled between November 1, 2017 and September 30, 2019. Off-label DOAC use was defined according to Food and Drug Administration prescribing information. Trained and audited data abstractors identified off-label DOAC prescribing using predefined data collection tools and a programmed alert. If these alerts occurred for actively prescribed medication-dose combinations, they were escalated to a MAQI[2] site lead (physician or pharmacist) for review. The study site lead was not contacted if the off-label DOAC error was no longer an active issue at the time of chart abstraction. Following MAQI[2] site lead verification, the DOAC prescribing clinician was contacted by the site lead. The result of prescribing clinician contact was obtained to determine any therapeutic change.

A waiver of informed consent was approved by the institutional review board at each participating site. Statistical analysis was performed using SAS software (version 9.4, Cary, NC) using *t* tests and Pearson's chi-square tests as appropriate. $P<0.05$ were considered significant. The data that support the findings of this study are available from the corresponding author on reasonable request.

Of the 2947 patients enrolled, mean age was 67.3 years and 48.2% were male. Atrial fibrillation was the most common DOAC prescribing indication (1554, 52.7%). The majority of the study population was prescribed apixaban (1848, 62.8%) or rivaroxaban (1077, 36.6%) The majority of patients were prescribed a DOAC by primary care (927, 31.5%) or cardiology (855, 29.0%) and most frequently as an inpatient (1762, 59.8%).

Off-label dosing occurred 308 times in 278/2947 (9.4%) patients (Table). Off-label DOAC dosing was more common among older patients, female patients, patients weighing less than 60 kg, and those with chronic kidney disease. Off-label prescribing was more common among patients using DOAC therapy for atrial fibrillation than venous thromboembolism. There was no significant difference in off-label DOAC prescribing by location (inpatient, outpatient, or emergency department). However, there was a difference in off-label usage among study sites.

Key Words: anticoagulant ■ anticoagulation ■ atrial fibrillation ■ deep vein thrombosis ■ pulmonary embolism

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Table. Patient Characteristics

	All Patients (n = 2947)	Off-Label Use (n = 278) (9.4% With 95% CI (8.4%, 10.6%)	On-Label Use (n = 2669)	*P* Value
Centers				
Center A	970 (32.9)	107 (38.5)	863 (32.3)	0.02
Center B	1060 (36)	98 (35.3)	962 (36)	
Center C	917 (31.1)	73 (26.3)	844 (31.6)	
Mean age (SD)	67.3±14.7	74.2±14.7	66.6±14.6	<0.001
Male (%)	1421 (48.2)	108 (38.9)	1313 (49.2)	0.001
Race/Ethnicity				
White	2295 (77.9)	226 (81.3)	2069 (77.5)	0.61
Black	454 (15.4)	34 (12.2)	420 (15.7)	
Asian	52 (1.8)	2 (0.7)	50 (1.9)	
Hispanic	14 (0.5)	2 (0.7)	12 (0.5)	
Native American	8 (0.3)	1 (0.4)	7 (0.3)	
Other/Not Reported	124 (4.6)	13 (4.7)	111 (4.2)	
Weight				
<60 kg	286 (9.7)	43 (15.5)	243 (9.1)	<0.001
60–140 kg	2559 (86.8)	231 (83.1)	2328 (87.2)	0.05
>140 kg	102 (3.5)	4 (1.4)	98 (3.7)	0.05
Indication				
Atrial fibrillation	1554 (52.7)	181 (65.1)	1373 (51.4)	<0.001
Venous thromboembolism	1100 (37.3)	93 (33.5)	1007 (37.7)	0.16
Other	308 (10.5)	10 (3.6)	298 (11.2)	<0.001
Direct oral anticoagulant				
Apixaban	1848 (62.8)	170 (61.4)	1678 (62.9)	0.008
Dabigatran	16 (0.5)	1 (0.4)	15 (0.6)	
Edoxaban	3 (0.1)	2 (0.7)	1 (0)	
Rivaroxaban	1077 (36.6)	104 (37.6)	973 (36.5)	
Prescriber specialty				
Cardiology	855 (29)	86 (30.9)	769 (28.8)	0.02
Emergency medicine	213 (7.2)	18 (6.5)	195 (7.3)	
Primary care (internal medicine or family medicine)	927 (31.5)	92 (33.1)	835 (31.3)	
Hematology	43 (1.5)	1 (0.4)	42 (1.6)	
Hospitalist	287 (9.7)	27 (9.7)	260 (9.7)	
Pulmonologist	24 (0.8)	4 (1.4)	20 (0.8)	
Surgeon	198 (6.7)	6 (2.2)	192 (7.2)	
Nurse practitioner/physician assistant	213 (7.2)	19 (6.8)	194 (7.3)	
Other	187 (6.4)	25 (9)	162 (6.1)	
Prescriber location				
Inpatient	1762 (59.8)	158 (56.8)	1604 (60.1)	0.39
Outpatient	880 (29.9)	93 (33.5)	787 (29.5)	
Emergency department	305 (10.4)	27 (9.7)	278 (10.4)	
Comorbidities				
Chronic kidney disease	360 (12.2)	66 (23.7)	294 (11)	<0.01
Cancer	735 (24.9)	90 (32.4)	645 (24.2)	0.003
Drugs				
Dual inhibitor of CYP3A4 and P-gp	7 (0.2)	4 (1.4)	3 (0.1)	<0.01
Dual inducer of CYP3A4 and P-gp	11 (0.4)	8 (2.9)	3 (0.1)	<0.01
P-gp inducer	11 (0.4)	8 (2.9)	3 (0.1)	<0.01
P-gp inhibitor	605 (20.5)	75 (27)	530 (19.9)	0.01

CYP3A4 indicates cytochrome P450 3A4; and P-gp, P-glycoprotein.

The most common off-label prescribing error was related to renal dysfunction or apixaban dosing criteria (169/308, 54.9%). DOAC use among patients with cirrhosis or Child-Pugh Class B or C liver disease was also common (51/308, 16.6%). DOAC dosing for the wrong indication occurred frequently (37/308, 12.0%) with atrial fibrillation dosing for venous thromboembolism (28/308, 9.1%) more common than venous thromboembolism dosing for atrial fibrillation (9/235, 2.9%). No patients with mechanical heart valves or moderate or severe mitral stenosis were identified among the DOAC population.

Of the 308 off-label DOAC prescribing errors identified, 81 (26.3%) were still inappropriate and deemed clinically relevant at the time of data abstraction. Contacting the prescribing clinician usually led to a meaningful change (51/81, 63.0%), with DOAC dose change, anticoagulant change, or concomitant drug discontinuation. However, many clinicians elected for no change (23, 28.4%). This was often justified by prescribers because of borderline/fluctuating renal function or weight.

Unlike prior studies reporting similar frequency of off-label DOAC use,[1,2] our study demonstrates a high degree of prescriber receptivity to being notified about the off-label prescription. Still, there were missed opportunities for intervention given delays in identification. Further studies are needed to explore how best to scale this approach for large health systems and populations.

One example for improving off-label DOAC use involves pharmacist-led anticoagulation services.[4] However, this approach may not be universally available or scalable to many health systems. Other options worthy of investigation include computerized methods to actively screen DOAC patients in real time. This would allow for immediate identification and rapid notification of prescribing clinicians. Similarly, smart prescribing alerts could be developed to guide clinicians in selecting on-label DOAC medications and doses at the time of initial prescription. These tools would require significant user-centered design to avoid issues of alert fatigue leading many clinicians to ignore these important messages. Regardless of the strategy, further risk reduction strategies are needed to optimize safe use of high-risk anticoagulant medications going forward. Ideally, decreasing inappropriate use should prevent adverse events, as has been shown related to renal dysfunction and DOAC dosing.[5]

In conclusion, off-label DOAC use remains common and is frequently related to renal dysfunction, apixaban dosing criteria, and advanced liver disease. Contacting the prescribing clinician frequently led to appropriate changes in drug selection, drug dose, or discontinuation of concomitant drug-drug interactions. Further studies are needed to explore how best to scale this approach for diverse health systems and populations, including the use of clinicians with various backgrounds, computerized screening methods, and well-designed prescribing alerts or order sets.

ARTICLE INFORMATION

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REFERENCES

1. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel J, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II Registry. *J Am Coll Cardiol*. 2016;68:2597–2604.
2. Tran E, Duckett A, Fisher S, Bohm N. Appropriateness of direct oral anticoagulant dosing for venous thromboembolism treatment. *J Thromb Thrombolysis*. 2017;43:505–513.
3. Sanghai S, Wong C, Wang Z, Clive P, Tran W, Waring M, Goldberg R, Hayward R, Saczynski JS, McManus DD. 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. DOI: 10.1161/JAHA.119.014108.
4. Leef GC, Perino AC, Askari M, Fan J, Ho PM, Olivier CB, Longo L, Mahaffey KW, Turakhia MP. Appropriateness of direct oral anticoagulant dosing in patients with atrial fibrillation: insights from the Veterans Health Administration. *J Pharm Pract*. 2019:897190019828270. DOI: 10.1177/0897190019828270.
5. Inohara T, Holmes DN, Pieper K, Blanco RG, Allen LA, Fonarow GC, Gersh BJ, Hylek EM, Ezekowitz MD, Kowey PR, et al. Decline in renal function and oral anticoagulation dose reduction among patients with atrial fibrillation. *Heart*. 2020;106:358–364.