



Letter to the Editors-in-Chief

Patient-level adherence and interventions in an interdisciplinary DOAC clinic



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ABSTRACT

Background: Direct oral anticoagulants (DOACs) are high risk medications with short half-lives making adherence vitally important. Global measures for adherence have been described; however, there is a lack of patient-level data on adherence.

Methods: This prospective, single-center study in an interdisciplinary internal medicine clinic included patients referred by their primary care physician for DOAC therapy evaluation. Patients were interviewed by a clinical pharmacist who confirmed dose and indication. Adherence was evaluated by asking how it was taken, at what time(s) of the day, and how many doses of their DOAC were missed. Labs and concomitant drugs were evaluated and patients received medication counseling. If any issues arose, the pharmacist would work together with the physician to resolve them.

Findings: Of 116 visits from 72 patients, an intervention was needed in 79 visits (68.1%). The most common problem identified was related to adherence: non-adherence to timing of dosing ($n = 30$), non-adherence to frequency of dosing ($n = 5$), and non-adherence to administration with food when indicated ($n = 11$). Adherence issues were present in 11 (61.1%) visits in patients taking rivaroxaban and 31 (33.0%) visits in patients taking apixaban.

Interpretation: An interdisciplinary DOAC service provided interventions for the majority of patients referred for DOAC therapy evaluation. The most frequent problem was non-adherence, with more than a third of patients found to be non-adherent to the timing of their medication administration.

1. Introduction

As the most common medication class responsible for emergency department visits anticoagulants are high risk medications [1]. Due to several advantages of direct oral anticoagulants (DOACs), including the lack of frequent laboratory monitoring, it is believed that patients on DOACs do not require close follow-up. However, patients remain at an increased risk of hemorrhagic and thromboembolic events if their anticoagulant is used improperly [2,3].

In general, studies evaluating adherence to DOACs are limited. Adherence is commonly assessed using global-level tools such as medication possession ratio (MPR) or prescription days covered (PDC) [4]. While global-level data is helpful, it may overestimate adherence. For example, in a study of patients taking vitamin K antagonists for atrial fibrillation and venous thromboembolism, global-level data showed 89.5% of patients were adherent while patient-level data showed that only 58.7% of patients were adherent [5]. Given the increased risk for adverse outcomes related to poor adherence it is imperative to accurately assess patient-level adherence in order to identify and address gaps in care for patients taking DOACs [2,6,7]. Therefore, we aimed to evaluate patient-level adherence in patients referred to our DOAC monitoring clinic.

2. Methods

This was a single-center, prospective study in an interdisciplinary academic internal medicine practice. All patients seen in the DOAC clinic between February 14th, 2017 to April 30th, 2018 were included.

Patients were referred by their primary care physician to the DOAC clinic for therapy evaluation and/or initiation. Patients met with a clinical pharmacist for an in-clinic visit focused on their DOAC. Adherence was evaluated by asking how many doses were missed on average and how/when the medication was taken. A full medication review was conducted to screen for drug-drug interactions. Labs were evaluated for safety and dosing and were reordered if necessary. Patients were assessed for symptoms of thrombosis or bleeding and counseled on their DOAC. If any changes were needed or if serious concerns arose, the pharmacist would communicate with the physician to jointly resolve the identified problem.

A standardized note template was utilized to ensure accuracy and consistency of patient interviews. Following each visit data was entered into REDCap, a secure web-based application for building and managing datasets (available via NCATS grant UL1 TR000064). Data was analyzed descriptively. The study was granted Continuous Quality Improvement status by our institution's ethics board. No funding was received from any source for this study.

3. Results

A total of 72 unique patients completing 116 visits were included in the analysis. At the index visit with the DOAC service the median age was 75.5 years (interquartile range [IQR] 70.0–81.3), most patients were female (43, 59.7%) and white (63, 87.5%) (Table 1). The most common DOAC utilized was apixaban (57, 79.2% of visits) and the most common indication was atrial fibrillation (57, 79.2% of visits) with a median CHA₂DS₂-VASc score of 4.0 (IQR 3.0–5.0).

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Table 1
Baseline characteristics.

	N = 72
Age (years), median (IQR)	75.5 (70.0–81.3)
Male sex, no. (%)	30 (41.1%)
Race, no. (%)	
White	64 (87.7%)
Black	5 (6.8%)
Asian	2 (2.7%)
Hispanic/Latino	1 (1.4%)
Other	1 (1.4%)
Weight (kg), median (IQR)	78.4 (64.7–96.5)
Calculated CrCl (ml/min), median (IQR)	53.5 (40.0–73.5)
DOAC, no. (%)	
apixaban	57 (78.0%)
rivaroxaban	14 (19.2%)
dabigatran	2 (2.7%)
Indication, no. (%)	
Acute DVT	6 (8.2%)
Chronic DVT	3 (4.1%)
Acute PE	7 (9.6%)
Chronic PE	2 (2.7%)
Atrial fibrillation	57 (78.1%)
Other	1 (1.4%)
CHA ₂ DS ₂ -VAsc for AF Only, median (IQR)	4.0 (3.0–5.0)

An intervention was needed in 79 visits (68.1%) with an average of 1.1 interventions per visit (Table 2). The average number of interventions decreased from 1.2 to 0.7 by visit 4. The most common problem identified was non-adherence (timing and/or frequency of medication administration or lack of administration with food, 45 visits), including 5 visits which identified a patient taking their medication once daily instead of twice daily.

In patients receiving rivaroxaban (18 total visits) a problem with adherence was identified in 11 visits (61.1% of rivaroxaban visits) with the most common problem involving lack of administration with meals. Of the visits conducted for patients receiving apixaban (94 visits) a problem with adherence was identified in 31 visits (33.0%) the majority of which were related to timing of administration. No adherence problems were identified with patients taking dabigatran (4 visits). Additional interventions made are noted in Table 2.

4. Discussion

This is the largest study of an outpatient DOAC monitoring service evaluating patient-level adherence. Frequently, the MPR or PDC are used to assess medication adherence over a large number of patients. However, these measures are imperfect as they do not have an ability to detect non-adherence at the patient level. In our analysis the use of MPR or PDC as a

marker for adherence, based on patient report, would have only identified a problem in 5 visits (4.3%) despite an adherence problem being identified through patient interview in 42 visits (36.2%). Given the narrow therapeutic index for DOACs combined with an increased risk for thrombosis with non-adherence, it is essential to ensure patients are taking their DOAC correctly by direct patient questioning [7].

Once daily administration for rivaroxaban is thought to improve adherence over twice daily DOACs such as apixaban or dabigatran. However, we found a higher rate of adherence problems for patients taking rivaroxaban (61.1% of rivaroxaban visits) compared to patients taking apixaban or dabigatran (31.6%).

The most common rivaroxaban-related adherence issue was lack of administration with food identified in 10 visits (55.5%). Notably, the prescription instructions included administration with food in only 11 of 16 visits (68.8%) for patients receiving rivaroxaban. Given that overall exposure to rivaroxaban 20 mg is increased by roughly 40% when it is administered with food, combined with the short half-life of 5–13 h, it is important to ensure patients administer it correctly for adequate protection against thrombotic events. Twenty-six visits identified an incorrect timing of administration for patients receiving apixaban but there were only 6 visits in which the prescription instructions were written as “every 12 hours.” All 6 cases involved the pharmacist preparing the prescription order. Notably, the missing instructions from prescriptions is a prescribing rather than an adherence issue. Therefore, prescribers of DOACs should, for example, strive to specifically indicate “every 24 hours with the evening meal” for rivaroxaban (for stable AF dosing) and “every 12 hours” with apixaban. Further, pharmacists dispensing DOACs should provide specific administration instructions to all patients no matter how long the patient has been receiving their DOAC.

Our study is not without limitations. First, our patient population was mostly white and from a single clinic so it is unclear if the problems found in our population would be generalizable to all patients. It is likely that populations with a higher percentage of non-white patients would show an even higher rate of non-adherence than seen in this study [8,9]. Patient referral was dependent on physicians and it is possible physicians were efficient at selecting the patients most at-risk for adherence-related problems. Further, we relied on the patient to report their adherence for our data collection and interventions. However, it is unlikely that our adherence rate was due to a large number of patients falsely identifying themselves as non-adherent. We also did not use a validated adherence questionnaire, such as the Morisky Medication Adherence Scale, as we wanted to tailor the questions specifically to DOACs as opposed to all medications. Lastly, as our sample size was relatively small and the study duration was limited we were unable to correlate DOAC monitoring to clinical outcomes. Future studies may include collaboration with other DOAC clinics, evaluation of clinical outcomes, and involvement of patient partners to further advance quality improvement.

Table 2
Interventions for all visits.

Interventions	1st Visit (N = 72)	2nd Visit (N = 28)	3rd Visit (N = 12)	4th Visit (N = 3)	5th Visit (N = 1)	Total of All Visits (N = 116)
Incorrect dose						
Incorrect dose - renal function	4	0	0	0	0	4
Incorrect dose - drug-drug interaction	3	0	0	0	0	3
Incorrect dose - indication	1	0	0	0	0	1
Adherence						
Adherence to dosing regimen – timing	22	7	1	0	0	30
Adherence to dosing regimen – frequency	4	0	1	0	0	5
Rivaroxaban not taken with dinner	9	2	0	0	0	11
Need for updated labs	24	9	3	2	1	39
Concomitant NSAID	4	1	0	0	0	5
Other	14	7	3	1	1	26
Total # interventions	85	26	8	3	2	124

In conclusion, an interdisciplinary outpatient DOAC service intervened in nearly 70% of visits. One of the most frequent interventions was related to medication adherence that would likely not have been accurately detected using global measures such as MPR or PDC. Further study is needed to determine if such interventions lead to a reduced rate of clinical events.

Declaration of interests

No conflicts of interest exist for any authors included on this publication that would have any potential to influence its content.

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