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Creatinine monitoring patterns in the setting of direct oral anticoagulant therapy for non-valvular atrial fibrillation

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Abstract

Guidelines and experts note that patients with atrial fibrillation require regular renal function monitoring to ensure safe use of direct oral anticoagulants (DOACs). Insufficient monitoring could lead to inappropriate dosing and adverse events. Our objective was to describe the frequency of insufficient creatinine monitoring among patients on DOACs, and to describe clinical factors associated with insufficient monitoring. We hypothesized that renal impairment would be associated with insufficient monitoring. A retrospective cohort study was performed with data from the Michigan Anticoagulant Quality Improvement Initiative. Patients were included if they initiated DOAC therapy for stroke prevention related to atrial fibrillation, remained on therapy for ≥ 1 year, and had baseline creatinine and weight measurements. Creatinine clearance (CrCl) was calculated via Cockcroft-Gault equation. Our outcome was the presence of insufficient creatinine monitoring, defined as: < 1 creatinine level/year for patients with CrCl > 50, or < 2 creatinine levels/year for patients with CrCl ≤ 50. Multivariable analysis was done via logistic regression. Study population included 511 patients. In overall, 14.0% of patients received insufficient monitoring. Among patients with CrCl > 50, 11.5% had < 1 creatinine level/year. Among patients with CrCl ≤ 50, 27.1% received < 2 creatinine levels/year. Baseline renal dysfunction was associated with a higher likelihood of insufficient creatinine monitoring (adjusted odds ratio 3.64, 95% confidence interval 1.81–7.29). This shows a significant gap in the monitoring of patients on DOACs—patients with renal impairment are already at higher risk for adverse events. Future studies are needed to describe the barriers in monitoring these patients and to identify how to optimally address them.

Keywords Atrial fibrillation · Creatinine · Factor Xa inhibitors · Kidney diseases · Drug monitoring

Highlights

- Atrial fibrillation patients on direct anticoagulants (DOACs) require renal function monitoring.
- It is unknown how many of these patients have creatinine monitoring according to guidelines.
- One in seven patients on DOACs for atrial fibrillation have insufficient creatinine monitoring.
- Baseline renal impairment was associated with higher risk of insufficient creatinine monitoring.
- Studies are needed to describe why this care gap exists and what steps would best address it.

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Introduction

Direct oral anticoagulants (DOACs) have become the standard of care for stroke prevention related to non-valvular atrial fibrillation (AF), given their efficacy, safety, and convenience as compared to warfarin [1, 2]. While DOACs do not require routine anticoagulation monitoring, they do require special attention to renal function [3].

A significant proportion of patients with AF have coexistent renal impairment or experience fluctuations in renal function while on treatment [1, 4]. At baseline, patients with comorbid AF and renal dysfunction are at higher risk for both thrombotic and bleeding events [5]. DOAC pharmacokinetics are influenced by kidney function; inappropriate dosing is also associated with a higher incidence of adverse events [3, 6]. For this reason, recommendations state that patients with AF should have a creatinine drawn before starting treatment, that patients with normal renal function have creatinine levels drawn annually, and that patients with renal impairment obtain more frequent monitoring [1, 2, 7–9].

A significant proportion of patients are started on DOAC therapy without a baseline creatinine or are dosed inappropriately due to fluctuations in renal function [4, 10]. Unfortunately, data on how clinicians longitudinally monitor patients' renal function while on DOACs is limited. Our study aimed to describe clinicians' creatinine monitoring patterns in the context of DOAC therapy, in addition to describing the relationship between various clinical factors and the possibility of receiving insufficient monitoring. Chief among these factors was the presence of pre-existing renal impairment. We hypothesized that patients with renal impairment would be more likely to receive insufficient monitoring.

Methods

This retrospective cohort study was conducted using previously collected data from the Michigan Anticoagulant Quality Improvement Initiative ($MAQI^2$), sponsored by Blue Cross Blue Shield of Michigan. Among the six $MAQI^2$ sites, four collect data on randomly selected patients initiating DOAC therapy. More details on $MAQI^2$ have been published previously [11, 12].

Our study size was determined by the maximum number of patients who met our inclusion criteria within the $MAQI^2$ database. For this analysis, we included patients (> 18 years old) who initiated DOAC therapy for stroke prevention in non-valvular AF. Patient enrollment spanned from November 2015–February 2017. Included patients needed to have a baseline weight, baseline creatinine, and ≥ 1 year of follow-up. Patients with creatinine clearance (CrCl) < 15 mL/min/1.73 m^2 were excluded since these patients are not eligible for DOAC therapy [1]. This cohort included patients on apixaban, rivaroxaban, and dabigatran; no patients were on edoxaban.

Demographic and clinical variables are abstracted from the medical record at the time of DOAC initiation and every 6 months thereafter. The follow-up period for each patient spanned from enrollment until data acquisition from the database in June 2018. Data was collected from the medical record by trained abstractors according to variable definitions defined previously by the $MAQI^2$ collaborative [11]. The $MAQI^2$ collaborative performs random audits to ensure accurate data abstraction. To describe our population, thromboembolic risk was quantified via CHA_2DS_2-VASC score; bleeding risk was quantified via HAS-BLED score [1, 13]. CrCl was calculated using the Cockcroft-Gault equation using actual body weight, as this method stratified patients by renal function in the DOAC clinical trials [14–17].

Our primary endpoint was the presence of insufficient creatinine monitoring. All guidelines recommend at least once yearly creatinine levels in patients without kidney dysfunction [2, 7–9]. It is generally recommended to obtain more frequent creatinine monitoring amongst patients with renal impairment; recommended intervals generally vary between every 3-6 months (Supplementary Table 1) [2, 7–9]. Given the retrospective nature of this study and our aim to describe natural clinical monitoring patterns, the physicians within these health systems were not given specific instructions on how to monitor renal function prior to collection of this data.

Our criteria defined insufficient monitoring as < 1 creatinine level/year for patients with CrCl > 50, or < 2 creatinine levels/year for patients with CrCl ≤ 50. Our analysis aimed to describe the prevalence of insufficient creatinine monitoring in our entire study population, and between patients with normal versus impaired renal function. We defined renal impairment as CrCl ≤ 50 since this is the threshold where DOAC dosing changes [3]. We performed two sensitivity analyses. In one analysis, the outcome was obtaining fewer than 1 creatinine level/year—to see if patients with renal impairment receive the same monitoring as other patients. In our other sensitivity analysis, we imposed stricter criteria for creatinine monitoring, approximating those given by the European Heart Rhythm Association (EHRA) [2]. In this analysis insufficient monitoring was considered: < 1 creatinine level/year for patients with CrCl > 60, < 2 creatinine levels/year for those with CrCl > 30–60, or < 3 creatinine levels/year for those with CrCl 15–30 [2]. Since EHRA guidelines recommend more frequent creatinine monitoring at CrCl of 60, renal impairment in this sensitivity analysis was defined as CrCl ≤ 60 [2].

Univariate comparisons were done via t test, Mood's median test, Fisher's exact test, and Chi square. To determine the relationship between clinical factors and creatinine monitoring, a multivariable logistical regression model was developed. Variables included baseline renal impairment, age, insurance status, DOAC used, comorbid heart failure, and comorbid hypertension. No effect modifier or interaction terms were included in our model. A two-sided $p < 0.05$ was considered statistically significant. All analyses were done in SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

We identified 1052 patients from the MAQI^2 registry on DOAC therapy for AF during the study period. Of those, 535 patients were excluded for having < 1 year of follow-up and 6 were excluded for missing data on enrollment or follow-up. Our final cohort was 249/511 (48.7%) male; mean age was 72.8 ± 11.0 years, 378/511 (74.0%) were on apixaban, and 85/511 (16.6%) had a baseline CrCl ≤ 50 (Table 1). Our study population is comparable to larger epidemiological cohorts in terms of age and racial makeup; our cohort has a higher female proportion and a lower proportion with renal impairment [18–20]. Patients were treated for a mean of 521.6 ± 149.4 days (Table 1).

Overall, 72/511 (14.1%) patients had insufficient creatinine monitoring. Patients with insufficient monitoring were on DOAC therapy longer than the patients with sufficient monitoring (Table 1). There were no significant differences in the choice of DOAC between classes of CrCl (Table 2). The median number of clinical encounters also did not differ between classes of CrCl (Table 2).

As shown in Table 2, 23/89 (27.1%) patients with CrCl ≤ 50 had insufficient renal monitoring, as compared to 49/246 (11.5%) of patients with CrCl > 50. In our multivariable analysis, baseline renal impairment was associated with higher odds of insufficient monitoring (adjusted odds ratio [aOR] 3.64, 95% confidence interval [CI] 1.81-7.29, Supplementary Table 2). Patients with heart failure were less likely to have insufficient monitoring (aOR 0.39, 95% CI 0.17–0.91, Supplementary Table 2). When using stricter monitoring criteria in our sensitivity analysis, 47/376 (12.5%) of patients with CrCl > 60 and 52/135 (38.5%) of patients with CrCl ≤ 60 received insufficient monitoring (data not shown). Having a CrCl ≤ 60 was associated with insufficient monitoring (aOR 5.05, 95% CI 2.84–8.96, Supplementary Table 3). Heart failure was associated with a lower likelihood of insufficient monitoring (aOR 0.49, 95% CI 0.24–0.98, Supplementary Table 3). Sensitivity analysis also demonstrated that patients with CrCl ≤ 50 and CrCl > 50 were similarly likely to have at least once yearly creatinine levels (aOR 0.61, 95% CI 0.22–1.75, Supplementary Table 4).

Discussion

In our cohort, one in seven patients had insufficient monitoring of their renal function while on DOAC therapy. Among patients with renal dysfunction, more than one in four patients did not receive twice-yearly creatinine testing, despite international guidelines recommending this in most chronic kidney disease (CKD) patients [9].

Our results demonstrate that many CKD patients who are treated with DOACs are not receiving frequent enough renal testing. Evidence on this topic has been scarce. A recent Spanish study observed that 39% of their patients received inadequate monitoring, and found decreasing CrCl to be associated with inadequate monitoring [21]. While similar results were found, national differences in the health care systems and guidelines limit the generalizability of this study to the United States [22]. To our knowledge, this is the first study to characterize these creatinine monitoring patterns in an American cohort. Our study provides data over a longer follow-up period and demonstrates a gap in care even when using lenient monitoring criteria. This is important—within a 2-year follow-up period, 12% of patients on DOACs had a change in renal function, a quarter of which was significant enough to require a dosage change [4]. Misdosing of DOACs has been associated with an increased risk of major bleeding, hospitalization, and death [6].

Strengths of this study include the use of chart abstracted and randomly audited data that reflects practice-based, unselected clinical patterns. Another strength is that our database includes data from four clinical sites, including academic and community-based centers. Our study does have limitations that warrant consideration. There is variation in recommendations for appropriate renal monitoring in DOAC patients, although we found that a considerable proportion of patients had insufficient monitoring by both strict and conservative definitions. Our sample size may limit the statistical power to detect weaker influences on creatinine monitoring. It is possible that these patients received creatinine testing outside of our database, although this is unlikely since all patients in MAQI^2-DOAC have primary care office records within our participating health care systems. Our study has limited generalizability among certain DOACs, including dabigatran and edoxaban, due to having few patients in the analysis. Finally, as with all observational studies, we cannot adjust for unmeasured confounders.

In summary, our results demonstrate an association between renal impairment and increased odds of insufficient creatinine monitoring. Future studies with larger populations should explore why this association occurs, what impact it

Table 1 Patient demographics and clinical characteristics, by level of creatinine monitoring

	Overall	Frequency of creatinine monitoring[a]	
		Sufficient	Insufficient
No. (%)	511	439 (85.9)	72 (14.1)
Age, mean (SD), years	72.8 (11.0)	72.6 (10.9)	74.2 (11.4)
Male, no. (%)	249 (48.7)	217 (49.4)	32 (44.4)
Race, no. (%)[b]			
Caucasian	430 (84.1)	374 (85.2)	56 (77.8)
Black	42 (8.2)	36 (8.2)	6 (8.3)
Other	22 (4.3)	17 (3.9)	5 (6.9)
Weight, mean (SD), kg	90.5 (25.6)	91.4 (26.2)	85.2 (20.3)
Insurance status, no. (%)			
Private	136 (26.6)	117 (26.7)	19 (26.4)
Medicaid	358 (70.1)	310 (70.6)	48 (66.7)
Unknown	17 (3.3)	2 (2.7)	5 (6.9)
CHA_2DS_2-VASc, mean (SD)	3.6 (1.6)	3.6 (1.5)	3.5 (1.7)
HAS-BLED, mean (SD)	2.7 (1.2)	2.7 (1.2)	2.5 (1.1)
Comorbidities, no. (%)			
Hypertension	435 (85.1)	370 (84.3)	65 (90.3)
Congestive heart failure	83 (16.2)	76 (17.3)	7 (9.7)
History of stroke	61 (11.9)	51 (11.6)	10 (13.9)
History of bleeds prior to DOAC*	160 (31.3)	145 (33.0)	15 (20.8)
Drug or alcohol use	22 (4.3)	21 (4.8)	1 (1.4)
DOAC used, no. (%)			
Apixaban	378 (74.0)	327 (74.5)	51 (70.8)
Rivaroxaban	124 (24.3)	104 (23.7)	20 (27.8)
Dabigatran	9 (1.8)	8 (1.8)	1 (1.4)
Duration of therapy at follow-up, mean (SD), days	521.6 (149.4)	513.5 (148.6)	571.2 (145.4)
Number of clinical encounters/year, median(IQR)	2.0 (2.0–2.0)	2.0 (2.0–2.0)	2.0 (2.0–2.0)
Initiated as inpatient, no. (%)	218 (42.7)	186 (42.4)	32 (44.4)
Prescriber specialty			
Cardiology	270 (52.8)	227 (51.7)	43 (59.7)
Primary care provider*	160 (31.3)	145 (33.0)	15 (20.8)
Other	81 (15.9)	67 (15.3)	14 (19.4)
Baseline CrCl, no. (%), mL/min/1.73 m^2			
> 50*	426 (83.4)	377 (85.9)	49 (68.1)
> 30–50*	76 (14.9)	54 (12.3)	22 (30.6)
15–30	9 (1.8)	8 (1.8)	1 (1.4)
Creatinine levels/year, median (IQR)*	2.0 (1.3–2.0)	2.0 (1.5–2.0)	0.67 (0.5–0.97)
NSAID, aspirin, antiplatelet use, no. (%)*	209 (40.9)	187 (42.6)	22 (30.6)
Loop diuretic use, no. (%)	9 (1.8)	8 (1.8)	1 (1.4)

*Statistically significant at alpha of 0.05

[a]Insufficient monitoring defined as < 1 creatinine level/year for patients with creatinine clearance (CrCl) > 50 mL/min, or < 2 creatinine levels/year for patients with CrCl ≤ 50 mL/min. CrCl estimated by Cockcroft-Gault

[b]The number of patients within racial categories does not add to the full population size since 17 patients had missing racial data

may have on clinical outcomes, and what steps would best mitigate this care gap.

Author contributions Concept and design: MMG, YL, EKR, MAA, SK, MD, JBF, GDB. Acquisition, analysis, or interpretation of data: YL, XK, DD. Drafting of the manuscript: MMG. Critical revision of the manuscript for important intellectual content: MMG, YL, XK, DD, EKR, MAA, SK, MD, JBF, GDB. Statistical analysis: YL, XK.

Table 2 Creatinine monitoring characteristics, by baseline renal function

	Baseline CrCl (mL/min/1.73 m^2)		
	> 50	> 30–50	15–30
No. (%)	426 (83.4)	76 (14.9)	9 (1.8)
Creatinine values/year, median (IQR)	2 (1–2)	2 (1.5–2)	2 (2–2)
Creatinine ≥ 1 time/year, no. (%)	377 (88.5)	71 (93.4)	9 (100)
Creatinine ≥ 2 times/year, no. (%)*	253 (59.4)	54 (71.1)	8 (88.9)
Number of clinical encounters/year, median (IQR)	2 (2–2)	2 (2–2)	2 (2–2)
DOAC used, no. (%)			
Apixaban	310 (72.8)	60 (78.9)	8 (88.9)
Rivaroxaban	107 (25.1)	16 (21.1)	1 (11.1)
Dabigatran	9 (2.1)	0	0

Creatinine clearance (CrCl) calculated by Cockcroft–Gault equation

*Statistically significant at alpha of 0.05

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Compliance with ethical standards

Conflict of interest Dr. Barnes reports grants from Pfizer/Bristol-Myers-Squib, Blue Cross Blue Shield of Michigan, National Heart Lung and Blood Institute during the conduct of the study. Dr. Barnes reports consulting fees from Pfizer/Bristol-Myers-Squib, Janssen, and Portola outside of the submitted work. Dr. Froehlich reports grant support from Blue Cross/Blue Shield of Michigan and the Fibromuscular Disease Society of America. Dr. Froehlich reports consulting fees for Merck, Janssen, and Novartis outside of the submitted work. Dr. Froehlich serves on the Advisory Committee of Boehringer-Ingelheim and Pfizer. Dr. Kaatz reports grants from Blue Cross Blue Shield of Michigan and Janssen during the conduct of the study. Dr. Kaatz reports consulting fees from Pfizer, Bristol Myer Squibb, Daiichi Sankyo, Portola, Roche, and Boehringer Ingelheim outside of the submitted work. Ms. Kline-Rogers reports consulting fees from Anticoagulation Forum and Janssen Pharmaceuticals outside of the submitted work. All other authors have no disclosures.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Given the retrospective nature of this study and the minimal risk that it presented to subjects, this study was granted a waiver of informed consent from our respective Institutional Review Board.

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