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RESEARCH LETTER

Unexplained hematuria in direct oral anticoagulant use: a single-center retrospective case series

1 | INTRODUCTION

Hematuria is a common presenting symptom of kidney, bladder, and ureteral cancers [1]. Urologic cancers are ultimately diagnosed in 10% to 20% of patients with gross hematuria, and 2% to 5% of patients with microscopic hematuria will go on to be diagnosed with a malignancy [1,2].

The American Urologic Association (AUA) 2012 guideline and 2020 AUA/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction, both recommended a urologic evaluation for any patient with hematuria (gross or microscopic), including patients who are currently prescribed anticoagulants [3,4]. Among patients not using anticoagulant medications, primary care physicians reported referring only 36% of patients with microhematuria and 69% to 77% of patients with gross hematuria to a urologist [5]. It is possible that rates of referral are even lower among patients using anticoagulant medications, given that hematuria is often thought to be a benign complication of anticoagulation therapy. Despite this misconception, bladder cancer is frequently diagnosed when a urology evaluation is performed among patients with anticoagulant-associated hematuria [6].

The objective of this study was to describe the real-world incidence and severity of hematuria in patients prescribed a direct oral anticoagulant (DOAC). We also describe how often a referral was made to urology, how often a urologic cancer was diagnosed, and how often DOACs were discontinued due to hematuria.

2 | METHODS

The Michigan Anticoagulation Quality Improvement Initiative (MAQI^2) is a Blue Cross Blue Shield, Blue Care Network of Michigan–sponsored quality improvement collaborative. Since 2015, funded abstractors at participating Michigan hospitals have entered patient data into a centralized online registry (MAQI^2-DOAC) with predefined variables. Baseline data from electronic medical records on randomly selected patients initiating a DOAC are entered into the registry. Follow-up reviews are conducted every 6 months to assess for adverse events.

We conducted a retrospective case series of adult patients from the MAQI^2-DOAC registry at a large academic medical center. At the time of data abstraction for this project, there were a total of 1676 adult patients entered into the registry at the participating site who were prescribed a DOAC for any indication between January 1, 2016, and December 31, 2022, with at least 6 months of follow-up. From this group, 143 patients had at least 1 episode of hematuria (microscopic or gross) and were analyzed. Eighty-eight patients were excluded because they were currently on a chemotherapy agent with the potential side effect of hematuria and/or hemorrhagic cystitis (3 patients; eg, cytoxan, regorafenib, oxaliplatin, and acalabrutinib); had undergone a recent urologic surgery (7 patients); or had a history of urologic cancer (22 patients; ie, prostate, bladder, kidney, and ureter), current urinary tract infection or kidney stone(s) (49 patients), or recent Foley catheter placement or intermittent self-catheterization (7 patients).

Data abstracted from the registry included demographics, indication for DOAC therapy, DOAC prescribed, severity of hematuria (International Society on Thrombosis and Haemostasis [ISTH] criteria) [7], and if the hematuria event required an emergency department (ED) visit. The University's electronic medical record search engine [8] was used to collect concomitant medications; medical history, including smoking status, urology consult, results of cystoscopy, if done; and if a new urologic cancer was diagnosed.

Descriptive statistics were reported without any inferential analysis.

The University's institutional review board (IRB) approved the study as an exempt review due to the retrospective nature of the study, and all the procedures being performed were part of the routine care. Consent to participate was not applicable since the University's IRB gave an exemption due to the retrospective nature of data collection. Consent for publication was not applicable since the University's IRB gave an exemption due to the retrospective nature of data collection.

3 | RESULTS AND DISCUSSION

One hundred forty-three DOAC-treated patients (143/1676, 8.5%) had at least 1 episode of hematuria, and 55/143 (38.5%) met all of the

inclusion criteria. Of these 55 patients, 31 (56.4%) were female, 28 (50.9%) had nonvalvular atrial fibrillation, 25 (45.5%) had venous thromboembolism, 25 (45.5%) were prescribed apixaban, and 30 (54.5%) were prescribed rivaroxaban. Only 1 patient (1.8%) was a current smoker, while 27 (49.1%) were former smokers (Table 1). All DOAC doses prescribed were appropriate with no off-label use.

Fourteen of the 55 patients (25.5%) had at least 1 recurrent minor hematuria event (Table 2).

All hematuria events were considered nonmajor in severity, with 10 patients (18.1%) presenting to the ED for hematuria. The majority of the patients (45/55, 81.8%) presented with gross hematuria (Table 1). No patient had the DOAC discontinued due to the hematuria.

A majority of the patients (29/55, 52.7%) were prescribed at least 1 concomitant medication that could increase bleeding risk: 20 patients (36.4%) were on CYP3A4 inhibitors and/or P-gP inhibitors, with 5 of these patients (25%) on more than 1 of these medications, and 11 patients (20%) were on aspirin. Nine of these 29 patients (31.0%) had a referral to urology (Table 1). Twenty-four patients (43.6%) had a referral to urology, resulting in cystoscopy procedures in 18 (75%). Of the patients who had a cystoscopy performed, 4 (22.2%) patients were found to have a newly diagnosed urologic cancer, including 3 with bladder cancers and 1 with renal cell carcinoma. Five of the 10 patients (50%) who went to the ED for hematuria had referrals placed to urology. Seven of the 10 patients (70%) who had microscopic hematuria were referred to urology (Table 2). Eleven of the 27 patients (40.7%) who were former smokers and the 1 current smoker were referred to urology (Table 1).

The patients diagnosed with bladder cancers all had gross hematuria. Of note, the 31/55 (56.4%) patients who did not have a referral to urology did not have a later diagnosis of a urologic cancer during their follow-ups.

Of the patients diagnosed with bladder cancer, 2 were former smokers, and the patient diagnosed with renal cell carcinoma was also a former smoker. All patients diagnosed with cancer were prescribed rivaroxaban.

Our retrospective case series of 55 patients with DOAC-associated hematuria found that less than half were referred for urologic evaluation, in spite of the 2012 AUA and 2020 AUA/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction recommendations. Furthermore, almost a quarter of patients undergoing cystoscopy were found to have a previously undiagnosed urologic cancer.

Hematuria is not only a complication of DOAC therapy but is a frequent complication of all antithrombotic therapies, and its association with subsequent cancer diagnosis can be remarkably high.

Smoking status is a well-known risk factor for urologic cancer development [9]. This aligns with our finding that 3 of the 4 patients eventually diagnosed with urologic cancer were former smokers. However, any unexplained DOAC-associated hematuria warrants urologic evaluation, even if the patient does not have a history of smoking.

TABLE 1 Patient characteristics.

Patient characteristics	Values, *n/N* (%)
Gender (female)	31/55 (56.4)
Race	
White	45/55 (81.8)
Black	7/55 (12.7)
Asian	3/55 (5.5)
Ethnicity	
Hispanic	2/55 (3.6)
Non-Hispanic	53/55 (96.4)
Age (y), mean/SD	68.2/23.93
DOAC indication	
NVAF	28/55 (50.9)
VTE	25/55 (45.5)
VTE prophylaxis	0/55 (0)
Other (ie, atrial tachycardia and superficial clot)	2/55 (3.6)
DOAC prescribed	
Apixaban	25/55 (45.5)
Rivaroxaban	30/55 (54.5)
Dabigatran	0/55 (0)
Edoxaban	0/55 (0)
Concomitant medications	
Aspirin	11/55 (20.0)
P2Y12	0/55 (0)
DAPT	0/55 (0)
NSAID	2/55 (3.6)
SSRI	3/55 (5.5)
CYP3A4 inhibitor and/or P-gP inhibitor	20/55 (36.4)
≥2 CYP3A4 inhibitor and/or P-gP inhibitor	5/20 (25.0)
Taking at least one concomitant medication and referred to urology	9/29 (31.0)
Smoking status	
Never	27/55 (49.1)
Referred to urology	12/27 (44.4)
Former	27/55 (49.1)
Referred to urology	11/27 (40.7)
Current	1/55 (1.8)
Referred to urology	1/1 (100)

DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SSRI, selective serotonin reuptake inhibitor; VTE, venous thromboembolism.

TABLE 2 Hematuria characteristics.

Hematuria characteristics	Values, *n/N* (%)
Hematuria severity	
ISTH-defined major	0/55 (0)
Nonmajor	55/55 (100)
Requiring ED visit	10/55 (18.1)
Referred to urology after ED visit	5/10 (50.0)
Urology evaluation	
Urology consult completed	24/55 (43.6)
Microscopic hematuria referred to urology	7/10 (70)
Cystoscopy completed after urology referral	18/24 (75.0)
Microscopic hematuria that had a cystoscopy	5/7 (71.4)
Type of hematuria	
Gross	45/55 (81.8)
Microscopic	10/55 (18.2)
Cancer diagnosis following first hematuria	
Bladder (all patients had gross hematuria)	3/4 (75.0)
Renal cell carcinoma (patient had microscopic hematuria)	1/4 (25.0)
Ureter	0/4 (0)
Prostate	0/4 (0)
Time of hematuria event from DOAC start	
0 to 6 mo	24/55 (43.6)
6 mo to 1 y	11/55 (20.0)
>1 y	20/55 (36.4)
Recurrent hematuria event	14/55 (25.5)
Patients with other bleeding event(s) during any follow-up	37/55 (67.3)
DOAC discontinued due to hematuria	0/55 (0)

DOAC, direct oral anticoagulant; ED, emergency department; ISTH, International Society on Thrombosis and Haemostasis.

As with all retrospective analyses, there are important limitations to consider. First, we report on a small number of patients from 1 academic health center in Michigan, which limits precision and generalizability. Our analysis is limited to apixaban and rivaroxaban use only; it may not be generalizable to other DOACs as our study site had no patients in the registry with hematuria and prescribed dabigatran or edoxaban. As with all observational studies, selection bias must be considered based on whom clinicians felt comfortable initiating apixaban or rivaroxaban therapy and where clinicians determined that urologic evaluation with cystoscopy was appropriate. Finally, we were unable to assess why some patients were referred to urology and others were not.

Despite these limitations, our study represents 1 of the first reports describing the lack of guideline-recommended urologic evaluation for patients with DOAC-associated hematuria. Our study also captures both gross and microscopic hematuria, including a more diverse population, and links outcomes to specific DOAC medications. Implementation efforts are needed to increase the use of guideline-recommended urologic evaluation, including assessments of effectiveness and cancer diagnosis yield.

ETHICS STATEMENT

The University's institutional review board (IRB) approved the study as an exempt review due to the retrospective nature of the study, and all the procedures being performed were part of the routine care. Consent to participate was not applicable since the University's IRB gave an exemption due to the retrospective nature of data collection. Consent for publication was not applicable since the University's IRB gave an exemption due to the retrospective nature of data collection.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation was performed by A.L. Material preparation, data collection, and analysis were performed by D.D.C., G.D.B., L.A.H., and B.H. The first draft of the manuscript was written by D.D.C. and G.D.B. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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