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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Clinical Significance of Hematuria in Atrial Fibrillation With Oral Anticoagulation Therapy

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Background: Hematuria is a common and important complication in atrial fibrillation (AF) patients on oral anticoagulation therapy (OAT). This study evaluated the clinical significance of hematuria and its relationship with genitourinary disease in AF patients receiving OAT.

Methods and Results: Among 20,456 consecutive AF patients who visited a tertiary hospital from January 2005 to April 2015, 5,833 had hematuria. Of these 5,833 patients, 3,798 were on OAT (OAT(+) group) and 2,035 were not (OAT(–) group). A total of 1,785 patients from each group were then matched on propensity score analysis. The prevalence of cancer and other diseases in the genitourinary tract was evaluated. While there was no difference in the prevalence of genitourinary stones or urinary tract infection, genitourinary cancer was significantly more common in the OAT(+) group than in the OAT(–) group (1.6% vs. 0.7%, P=0.011). Bladder cancer was the most common genitourinary malignancy, and it was significantly more common in the OAT(+) group (1.2% vs. 0.5%, P=0.019). Subjects on warfarin were more likely to have bladder cancers of lower pathologic grade (63.6% vs. 33.3%, P=0.124).

Conclusions: OAT was associated with a higher prevalence and early detection of genitourinary cancer in AF patients with hematuria. Meticulous evaluation of the cause of hematuria is necessary in AF patients with hematuria receiving OAT.

Key Words: Anticoagulation; Atrial fibrillation; Genitourinary cancer; Hematuria; Warfarin

Atrial fibrillation (AF) is a major contributing factor in stroke and is associated with a 5-fold increase in incidence.[1,2] Thus, stroke prevention is an important factor in clinical management of AF. Multiple clinical trials have demonstrated the superior therapeutic effect of oral anticoagulation therapy (OAT) with warfarin in the prevention of stroke in patients with non-valvular AF.[3–5] Therefore, current guidelines recommend OAT in non-valvular AF with intermediate–high risk of stroke.[2,6] A growing number of patients receiving OAT, however, subsequently develop bleeding complications such as intracranial hemorrhage, gastrointestinal bleeding, or hematuria. Bleeding is the most important complication of OAT and is a major concern for both clinicians and patients. One of the most common sites of bleeding is the genitourinary tract, with a previous study reporting an incidence of 40% in anticoagulated patients.[7] The presence of anticoagulant-associated hematuria is frequently related to the underlying genitourinary pathology.[8,9] In patients undergoing urological evaluation for hematuria while receiving OAT, this etiology is found in 3–82% of cases.[9–13] Previous studies have suggested that anticoagulated patients with gross hematuria have a high frequency of major underlying disease such as urolithiasis, infection, congenital anomaly, and malignancy.[9,11,13,14] Furthermore, in some forms of malignancy such as stomach or colorectal cancer, anticoagulant-related gastrointestinal bleeding was found to facilitate early detection of malignant gastrointestinal lesions.[15,16] Thorough evaluation of anticoagulant-related bleeding is critical to detect malignancy during the potential window of curability,[17] but, although hematuria is not an uncommon complication in patients with OAT, there are limited data on the impact of anticoagulation on evaluation and management.[10,12]

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Thus, the aim of the present study was to examine the clinical significance of hematuria and its relationship with genitourinary disease in AF patients receiving OAT. Moreover, we evaluated whether OAT could influence early diagnosis of the disease.

Methods

Study Design

This study enrolled patients who visited and/or were admitted to a tertiary hospital in Korea with a principal

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diagnosis of AF from January 2005 through April 2015. All data were obtained from the Clinical Data Repository System (CDRS), a hospital database used primarily for research and administrative purposes. All clinical variables were confirmed by the presence and date of the initial diagnosis in CDRS. Using International Classification of Diseases 10th Revision (ICD-10) codes, we identified 20,456 consecutive patients with AF (I48.0) aged >18 years (**Figure 1**). This study included only patients with microscopic or gross hematuria (n=5,833). We divided these patients into 2 groups consisting of those with OAT (OAT(+), n=3,798) and those without OAT (OAT(−), n=2,035). Warfarin was the oral anticoagulant prescribed for all patients in the OAT(+) group. A non-vitamin K antagonist oral anticoagulant (NOAC) was not included in this study. Patients who were started on OAT before AF diagnosis were excluded. Patients who were diagnosed with genitourinary tract disease prior to detection of hematuria were also excluded from analysis. Baseline demographics such as age, gender, height, weight, and body mass index (BMI) were analyzed, and the congestive heart failure (CHF), hypertension, age ≥75 (doubled), diabetes mellitus (DM), prior stroke or transient ischemic attack (TIA; doubled), vascular disease, age 65–74 years and sex category (female) (CHA_2DS_2-VASc) score and the hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (age >65 years), drugs/alcohol concomitantly (HAS-BLED) scores were evaluated.

Propensity scores were used to match the patients with OAT to those without to reduce the potential confounding in this observational study (**Figure 1**). Propensity scores were estimated using a non-parsimonious multiple logistic regression model for the OAT(+) and OAT(−) groups. The following variables were entered: age, sex, and history of CHF, hypertension, DM, stroke or TIA, and vascular disease. Cases were matched, without replacement, with controls based on the closest possible value of the propensity score (nearest neighbor matching). A matching caliper of 0.1 SD of the logit of the estimated propensity score was enforced to ensure that matches of poor fit were excluded. The matching procedure was performed using the R packages Matchit, RItools, and CEM (R Foundation for Statistical Computing, Vienna, Austria).[18] The study protocol was approved by the Institutional Review Board of Severance Cardiovascular Hospital, Seoul, Korea, and adhered to the principles of the Declaration of Helsinki.

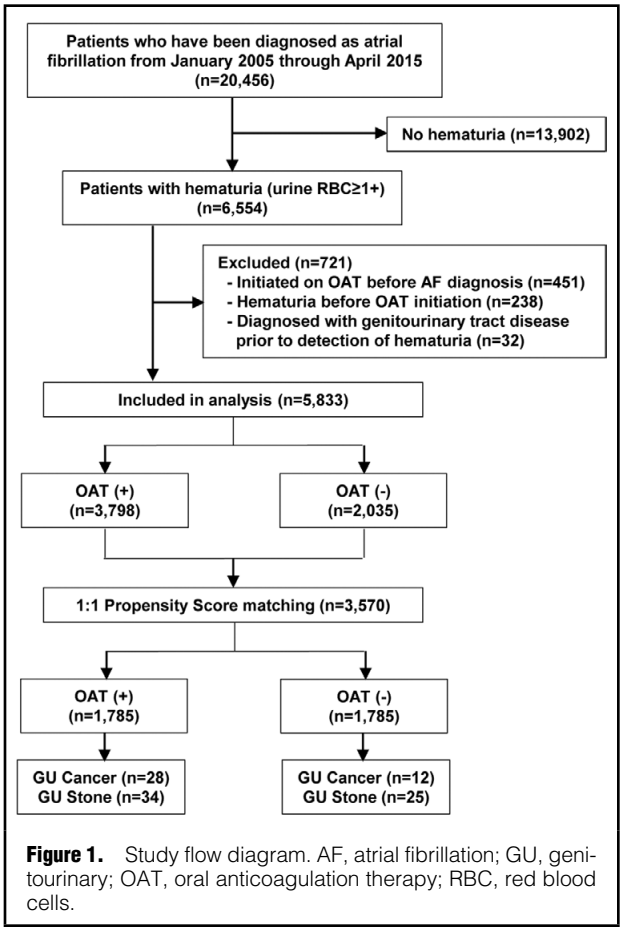

Figure 1. Study flow diagram. AF, atrial fibrillation; GU, genitourinary; OAT, oral anticoagulation therapy; RBC, red blood cells.

Hematuria Definition

Hematuria was identified using ICD-10 codes R31.0, R31.1, R31.8, and N02.9 and random urinalysis. Microscopic hematuria was detected using standard urine dipstick (Siemens Multistix 10SG, Siemens Healthcare Diagnostics, Tarrytown, NY, USA). Hemoglobin concentration 0.015–0.062 mg/dL (150–620 μg/L) was taken as the equivalent of approximately 5–20 intact red blood cells (RBC)/μL, and the degree of microscopic hematuria ranged from urine RBC 0 to 3+. The highest urine RBC level during the search period was used in analysis. Gross hematuria was defined as macroscopic hematuria requiring hospital admission. Patients who developed hematuria before OAT initiation were excluded from analysis.

Clinical Outcomes and Measures

The prevalence of genitourinary tract malignancy (kidney [ICD-10 code C64], ureter [ICD-10 code C66], and bladder [ICD-10 code C67]), genitourinary tract stones (kidney [ICD-10 code N20.0], ureter [ICD-10 code N20.1], and bladder [ICD-10 code N21.0]), benign prostatic hyperplasia (BPH; ICD-10 code N40.0), prostatitis (ICD-10 code N41.9), and urinary tract infection (UTI; ICD-10 code N39.0) was evaluated. The criteria for diagnosis were pathologic documentation and evidence of genitourinary cancer and/or stones on simple radiology, computed tomography, ultrasound, and endoscopy. In patients with bladder cancer, histopathological classification of tumor grade followed the World Health Organization/International Society of Urological Pathology consensus classification of urothelial neoplasms of the urinary bladder.[19] Low-grade papillary urothelial carcinoma was defined as neoplasm of the urothelium lining papillary fronds with an orderly appearance but easily recognizable variations in architecture and cytologic features. High-grade papillary urothelial carcinoma was defined as neoplasm of the urothelium lining papillary fronds with a predominant pattern of disorder with moderate-to-marked architectural and cytologic atypia.

Statistical Analysis

Continuous variables are expressed as mean±SD and were compared using Student's t-test and ANOVA. Categorical variables are reported as frequencies (percentage) and were compared using the chi-squared or Fisher's exact test. The matched patient groups were compared using the paired

Table 1. Subject Clinical Characteristics

	Total			Propensity score matched		
	OAT(+) (n=3,798)	OAT(−) (n=2,035)	P-value	OAT(+) (n=1,785)	OAT(−) (n=1,785)	P-value
Age (years)	67±12	69±13	<0.001*	68±12	68±12	0.689
Female	1,980 (52.1)	928 (45.6)	<0.001*	860 (48.2)	845 (47.3)	0.639
BMI (kg/m^2)	23.3±3.7	22.9±3.7	0.033*	23.2±3.5	23.1±3.6	0.734
CHF	985 (25.9)	278 (13.7)	<0.001*	206 (11.5)	221 (12.4)	0.470
Hypertension	2,237 (58.9)	1,058 (52.0)	<0.001*	988 (55.4)	977 (54.7)	0.737
65≤Age<74 years	1,369 (36.0)	683 (33.6)	0.062	640 (35.9)	642 (36.0)	0.972
Age ≥75 years	1,068 (28.1)	694 (34.1)	<0.001*	550 (30.8)	558 (31.3)	0.800
Diabetes	675 (17.8)	285 (14.0)	<0.001*	224 (12.5)	234 (13.1)	0.652
Stroke/TIA	593 (15.6)	325 (16.0)	0.734	261 (14.6)	291 (16.3)	0.179
Vascular disease	397 (10.5)	204 (10.0)	0.619	178 (10.0)	179 (10.0)	0.956
CHA_2DS_2-VASc score	2.7±1.8	2.6±1.8	0.028*	2.6±1.8	2.6±1.8	0.728
HAS-BLED score	2.2±1.3	2.1±1.3	0.041*	2.1±1.3	2.1±1.3	0.657
Aspirin	1,357 (35.7)	826 (40.6)	<0.001*	639 (35.8)	726 (40.7)	0.003*
Clopidogrel	961 (25.3)	473 (23.2)	0.085	448 (25.1)	414 (23.2)	0.197
Hematuria grade			0.001*			0.141
Urine RBC 1+	1,100 (29.0)	657 (32.3)		549 (30.8)	588 (32.9)	
Urine RBC 2+	1,229 (32.4)	687 (33.8)		599 (33.6)	614 (34.4)	
Urine RBC 3+	1,339 (35.3)	642 (31.5)		575 (32.2)	538 (30.1)	
Gross	130 (3.4)	49 (2.4)		62 (3.5)	45 (2.5)	

Data given as n (%) or mean±SD. *P<0.05. BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74 years and sex category (female); CHF, congestive heart failure; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age >65 years), drugs/alcohol concomitantly; OAT, oral anticoagulation therapy; RBC, red blood cells; TIA, transient ischemic attack.

Table 2. GU Disease Type vs. Presence of OAT

	Total			Propensity score matched		
	OAT(+) (n=3,798)	OAT(−) (n=2,035)	P-value	OAT(+) (n=1,785)	OAT(−) (n=1,785)	P-value
GU cancer	65 (1.7)	13 (0.6)	0.001*	28 (1.6)	12 (0.7)	0.011*
GU stone	71 (1.9)	28 (1.4)	0.164	34 (1.9)	25 (1.4)	0.237
BPH/prostatitis	218 (5.7)	101 (5.0)	0.227	102 (5.7)	87 (4.9)	0.295
UTI	260 (6.8)	116 (5.7)	0.093	118 (6.6)	104 (5.8)	0.368
Undetermined	1,389 (36.6)	658 (32.3)	0.001*	632 (35.4)	584 (32.7)	0.097
No evaluation	1,795 (47.3)	1,119 (55.0)	<0.001*	871 (48.8)	973 (54.5)	0.001*

Data given as n (%). *P<0.05. BPH, benign prostatic hyperplasia; GU, genitourinary; OAT, oral anticoagulation therapy; UTI, urinary tract infection.

t-test for continuous variables and the McNemar test for categorical variables. The strength of the association between covariates and the presence of genitourinary cancers are expressed as OR with 95% CI. SPSS 20.0 (SPSS, Chicago, IL, USA) was used to perform all statistical evaluations. Two-tailed P<0.05 was considered statistically significant.

Results

Clinical Characteristics

The baseline characteristics of the OAT(+) and OAT(−) groups are summarized in **Table 1**. Patients with OAT were younger (67±12 years vs. 69±13 years, P<0.001), tended to be female (52.1% vs. 45.6%, P<0.001), had higher BMI (P=0.033), CHA_2DS_2-VASc score (P=0.028), and HAS-BLED score (P=0.041), had higher prevalence of CHF (P<0.001), hypertension (P<0.001), and DM (P<0.001), and had a lower prevalence of aspirin use (P<0.001) than those not receiving OAT. With regard to the whole groups, gross hematuria (P=0.032) or urine RBC 3+ hematuria (P=0.004) was observed significantly more frequently in the OAT(+) than the OAT(−) group. After 1-to-1 propensity score matching, baseline characteristics were well matched, except for the prevalence of aspirin use (P=0.003) between the 2 groups. The distribution of hematuria grading was similar between the OAT(+) and OAT(−) group on propensity score matching.

Genitourinary Tract Disease vs. Presence of OAT

Table 2 lists the frequency of genitourinary tract diseases in AF patients according to the presence of OAT.

Genitourinary cancer was diagnosed more frequently in patients taking OAT: 65 (1.7%) with vs. 13 (0.6%) without OAT (P=0.001). With regard to the 2 whole groups, there were no significant differences in the prevalence of genitourinary stones (1.9% vs. 1.4%, P=0.164), BPH or prostatitis (5.7% vs. 5.0%, P=0.227), or UTI (6.8% vs. 5.7%, P=0.093) between groups. On propensity score matching, genitourinary cancer was still significantly more common in the OAT(+) group compared with OAT(−) group (1.6% vs. 0.7%, P=0.011). The results did not change when aspirin and clopidogrel use were included in the propensity score matching (1.8% vs. 0.6%, P=0.001). There were no significant differences in the prevalence of genitourinary stone (1.9% vs. 1.4%, P=0.237), BPH or prostatitis (5.7% vs. 4.9%, P=0.295), or UTI (6.6% vs. 5.8%, P=0.368) between the 2 propensity score-matched groups.

Hematuria vs. Time After OAT Initiation

The proportion of patients who had hematuria according to genitourinary cancer type vs. the time since OAT initiation is presented in **Figure 2**. In a total of 65 patients with genitourinary cancer, 17 (26.2%) had hematuria within the first 2 months after the initiation of OAT. One year after OAT initiation, the annual incidence of hematuria was approximately 3–12%. This trend was also consistent with other genitourinary pathologies, such as genitourinary stone, BPH, UTI, and so on.

Genitourinary Cancer Site

The bladder was the most common site of cancer detection (**Figure 3**). In the 2 whole groups, bladder cancer was significantly more common in the OAT(+) group (1.2% vs. 0.4%, P=0.004), while there was no difference in the frequency of renal (0.3% vs. 0.1%, P=0.226) or ureter (0.2% vs. 0%, P=0.098) cancer between the 2 groups (**Figure 3A**). After propensity score matching, bladder cancer was still more common in the OAT(+) group than in the OAT(−) group (1.2% vs. 0.5%, P=0.019; **Figure 3B**). There was no difference in the frequency of renal (0.1% vs. 0.1%, P=0.564) or ureter (0.3% vs. 0.1%, P=0.102) cancer between the 2 propensity score-matched groups.

Genitourinary Cancer Pathologic Grade

We additionally evaluated the pathologic grade of bladder cancer, which was the most common lesion of the genitourinary malignancies. In patients with bladder cancer, subjects who were taking warfarin were more likely to have low pathologic grade papillary urothelial tumors compared with those who were not taking anticoagulants (65.2% vs. 33.3%, P=0.074), although these differences were not statistically significant (**Figure 4A**). This tendency towards early detection of bladder cancer was also found in the propensity score-matched groups (63.6% vs. 33.3%, P=0.124; **Figure 4B**).

Risk Factors of Genitourinary Cancer in OAT Patients

We determined the proportion of patients in the whole OAT(+) group who had genitourinary cancer according to demographic and clinical characteristics (**Table 3**). In the logistic model for genitourinary cancer, old age (age ≥75 years, compared with age <65 years: OR, 3.58; 95% CI: 1.16–11.04, P=0.027), male sex (OR, 2.83; 95% CI: 1.20–6.69, P=0.018), and higher urine RBC grading (urine RBC 3+, compared with urine RBC 1+: OR, 7.33; 95% CI: 1.67–32.2, P=0.008) or gross hematuria (compared with urine RBC 1+: OR, 40.5; 95% CI: 8.39–195.64, P<0.001) were significantly associated with an increased risk of genitourinary cancer in AF patients with hematuria who were taking warfarin.

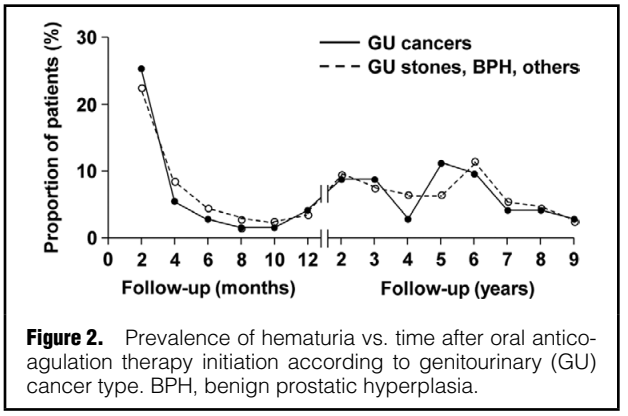

Figure 2. Prevalence of hematuria vs. time after oral anticoagulation therapy initiation according to genitourinary (GU) cancer type. BPH, benign prostatic hyperplasia.

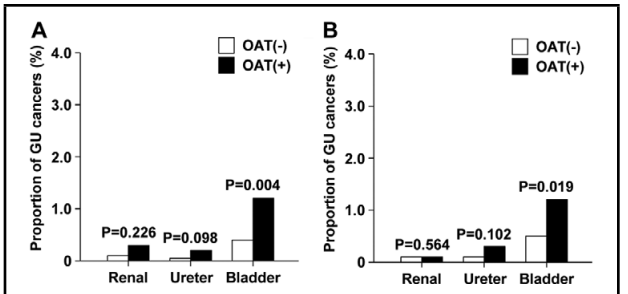

Figure 3. Location of genitourinary (GU) cancer in hematuria patients in (**A**) the total and (**B**) propensity score-matched oral anticoagulation therapy (OAT)(+) and OAT(−) groups.

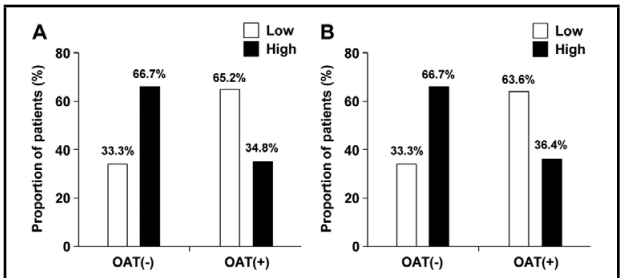

Figure 4. Pathologic grade of bladder cancer in (**A**) the total and (**B**) propensity score-matched oral anticoagulation therapy (OAT)(+) and OAT(−) groups.

Discussion

Main Findings

In the present study, we evaluated the clinical significance of hematuria in AF patients taking OAT. First, genitourinary cancer was more common in patients with OAT compared with those without, in the whole groups and after propensity score matching. OAT, however, was not associated with hematuria severity. Second, bladder cancer was

Table 3. Prevalence of GU Cancer in OAT(+) AF Patients With Hematuria

Characteristics	GU cancer (%)	OR (95% CI)	P-value
Age (years)			
<65	0.7	1.000 (Ref.)	
65–74	1.7	2.584 (0.818–8.159)	0.106
≥75	2.4	3.577 (1.159–11.036)	0.027*
Gender			
Female	0.8	1.000 (Ref.)	
Male	2.3	2.831 (1.197–6.693)	0.018*
CHF			
No	1.6	1.000 (Ref.)	
Yes	1.0	0.586 (0.138–2.486)	0.468
Hypertension			
No	1.3	1.000 (Ref.)	
Yes	1.8	1.460 (0.670–3.182)	0.340
Diabetes			
No	1.5	1.000 (Ref.)	
Yes	2.2	1.527 (0.574–4.057)	0.396
Stroke/TIA			
No	1.6	1.000 (Ref.)	
Yes	1.1	0.697 (0.209–2.326)	0.557
Vascular disease			
No	1.6	1.000 (Ref.)	
Yes	1.1	0.691 (0.163–2.936)	0.617
Antiplatelet use			
No	1.9	1.000 (Ref.)	
Yes	1.2	0.611 (0.275–1.359)	0.227
Hematuria grade			
Urine RBC 1+	0.4	1.000 (Ref.)	
Urine RBC 2+	0.5	1.377 (0.229–8.270)	0.727
Urine RBC 3+	2.6	7.326 (1.667–32.186)	0.008*
Gross	12.9	40.519 (8.392–195.638)	<0.001*

*P<0.05. AF, atrial fibrillation. Other abbreviations as in Tables 1,2.

the most common genitourinary malignancy and was significantly more common in the OAT(+) group than in the OAT(−) group. Third, patients in the OAT(+) group were more likely to have bladder cancers of low pathologic grade, suggesting early detection of the malignancy. Finally, age >75 years, male sex, and hematuria grade of urine RBC 3+ or gross hematuria were associated with increased risk of genitourinary cancer. Meticulous evaluation of the cause of hematuria should therefore be carried out in AF patients receiving OAT and presenting with hematuria, especially in aged, male subjects with high hematuria.

Hematuria and Genitourinary Tract Disease

Hematuria is a common urological presentation with an estimated prevalence of 5–20% of all urological visits.[20] Asymptomatic gross hematuria is a common and important finding in patients with genitourinary cancer, especially bladder cancer, with 70–80% of these patients having hematuria on initial presentation.[21,22] In a prospective analysis in patients with either microscopic or gross hematuria, approximately 40% of patients had an identifiable pathology associated with hematuria, consisting of bladder cancer (12%), renal cancer (0.6%), UTI (13%), genitourinary tract stones (2%), or benign renal disease (10%).[23] In the present study, the cause of hematuria was genitourinary tract malignancy in 1.1%, stone disease in 1.7%, BPH or prostatitis in 5.3%, and UTI in 6.2% of cases in the propensity score-matched groups. No cause for hematuria was found in 34.1% of cases. These findings are similar to those of one of the largest prospective hematuria studies, in which 61% of patients with hematuria had no underlying cause.[23]

Clinical Significance of Hematuria in OAT Patients

Considering the growing number of patients receiving OAT for various indications,[24,25] clinicians are likely to be faced with an increasing number of patients presenting with hematuria. In addition, the effect of NOAC on genitourinary bleeding may be different from that of warfarin. The significance of hematuria in patients receiving OAT, however, has been addressed only by several small studies, which were conducted in relatively small samples of <100 patients. In these studies, genitourinary tract pathology including carcinoma, calculi, renal infarction, and/or infection was noted in 30–60% of patients taking warfarin and presenting with hematuria, with considerable variance between studies.[9,13,14] The strengths of the present study are the relatively large sample size, and the inclusion of a propensity score-matched control group of patients who were not taking warfarin. This study emphasizes the importance of complete evaluation of hematuria in patients receiving anticoagulation therapy.

OAT and the Detection of Genitourinary Cancer

Although the primary presentation of genitourinary cancer is hematuria (microscopic or gross), the presence of concomitant OAT may lead clinicians to underestimate this finding, given that bleeding is not an uncommon complication with anticoagulation therapy.[26,27] Accordingly, in patients receiving OAT who develop hematuria, malignancy is not usually suspected and complete evaluation of the genitourinary tract may be considerably delayed. In the present study, hematuria was associated with a significantly higher incidence of genitourinary cancer in patients with OAT compared with those without.

In contrast, there is evidence that warfarin has anticancer properties in some types of malignancy. In population-based observational studies, long-term use of warfarin was associated with a lower incidence of prostate cancer,[28–30] but these trials did not show a difference in the incidence of renal or bladder cancer according to warfarin use. The reason why a protective effect was not seen for the other types of genitourinary cancer is unclear, and further study is needed with a more complete assessment of confounders in a larger subject group.

Another interesting finding was the increased frequency of low-grade papillary urothelial cancers in patients with OAT compared with those without OAT. In the present bladder cancer patients, 63.6% of those in the OAT group and 33.3% of the control subjects (i.e., OAT(−) group) had early cancer (low pathologic grade of papillary urothelial carcinoma). This is clinically important because there were significant differences in the progression and cancer-specific mortality cumulative incidence between the low- and the high-grade papillary urothelial carcinomas.[31] The earlier detection of genitourinary cancer in patients with OAT may be explained by the OAT-enhanced bleeding in patients with low-grade lesions that otherwise would not have been diagnosed. This hypothesis is supported by

several previous reports that describe early diagnosis of colorectal cancer in patients with warfarin-associated gastrointestinal bleeding.[15,32,33] These findings must be interpreted with caution, however, because of the small number of patients with bladder cancer in the present study. Bleeding may be the first sign of significant genitourinary pathology in patients receiving OAT, and therefore evaluation of the upper and lower urinary tract is warranted in this patient group.

Study Limitations

The present study had several limitations. First, this was a retrospective observational study that utilized CDRS data on a large number of patients. Although large-scale databases are increasingly used for clinical research, such studies are potentially susceptible to errors arising from coding inaccuracies. To minimize this problem, we analyzed medical data in patients with clinical outcomes including malignancy, stone and other urological pathologies. Second, clinical characteristics differed between patients with and without OAT. To reduce the effects of unmeasured confounders, we carried out propensity score matching that included many clinical variables. Third, almost half of the study patients did not receive evaluation of the cause of hematuria. Thus the present incidence of genitourinary tract disease might have been underestimated. Finally, the information on the level of anticoagulation, which may strongly affect the possibility of bleeding, was not available for analysis. Despite these limitations, the present study has considerable strengths resulting from the analysis of a large sample size derived from a real world database.

Conclusions

OAT was associated with a higher prevalence and early detection of genitourinary cancer in patients with AF who had hematuria. Meticulous evaluation of the cause of hematuria should be performed in AF patients receiving OAT and presenting with hematuria.

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Disclosures

The authors declare no conflicts of interest.

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