# *Does antithrombotic use enable earlier diagnosis of bladder cancer? A brief institutional assessment*

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***Introduction:*** *Wallis et al (JAMA 2017) demonstrated use of antithrombotic medications (ATMs) is associated with increased prevalence of hematuria-related complications and subsequent bladder cancer diagnosis within 6 months. Stage of diagnosis was lacking in this highly publicized study. This study examined the association of ATM use on bladder cancer stage at the time of diagnosis.*

***Materials and methods:*** *We completed a retrospective chart review of patients with a bladder cancer diagnosis at our institution. Patient demographics and bladder cancer work up information were assessed. Patients were stratified based on use of ATMs at time diagnosis. Descriptive statistics were completed to identify association between ATM use and stage of bladder cancer diagnosis, as stratified by non-muscle invasive bladder cancer (NMIBC) versus muscle invasive bladder cancer (MIBC).*

***Results:*** *A total of 1052 patient charts were reviewed. Eight hundred and forty-four were included and 208 excluded due to unavailability of diagnosis history. At diagnosis, 357 (42.3%) patients were taking ATMs. Patients on ATMs presented with NMIBC at similar rates as patients not taking ATMs (81.2% vs. 77.8%, p = 0.23). Subgroup analysis by ATM class similarly demonstrated no statistically significant differences in staging.*

***Conclusion:*** *While Wallis et al established that patients on blood thinners who present with hematuria are more likely to be diagnosed with genitourinary pathology, this factor does not appear to enable an earlier diagnosis of bladder cancer. Future study may assess hematuria at presentation (gross, microscopic), type of blood thinners, and low versus high risk NMIBC presentation.*

**Key Words:** bladder cancer, hematuria, antithrombotic medications, anti-coagulation, cancer staging

## Introduction

Bladder cancer is the second most common urologic malignancy in the Western hemisphere, and a quarter of bladder cancer patients are diagnosed with locally advanced, muscle invasive, or metastatic disease.[1] Delayed diagnosis increases mortality, treatment morbidity, and cost, but identification of early stage bladder cancer is difficult, and adequate screening methods are lacking.

Most bladder cancer diagnoses result from patient presentation with hematuria (gross or microscopic), which is experienced by one-fifth of the general population during their lifetime.[2] Antithrombotic medication (ATM) use is a commonly cited cause of

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hematuria. Wallis et al demonstrated that patients on chronic ATM therapy experience more hematuria-related complications, and importantly, face a doubled risk of uncovering a subsequent bladder cancer diagnosis versus the general population.[3] However, an earlier study found no association between anticoagulants and hematuria, and a more recent analysis reported equal risk of cancer diagnosis in hematuria patients with or without ATMs.[4,5] These contradictions warrant further investigation of the association between ATM-associated hematuria and bladder cancer diagnosis, particularly given the rapid evolution in modern anticoagulant and antiplatelet pharmacology. Although ATM use may not directly cause bladder cancer, it may facilitate diagnosis by precipitating hematuria.

Understanding the interaction between ATMs and ease of bladder cancer diagnosis is important. Bladder cancer risk factors, including smoking and advanced age, are concurrently hazards for conditions treated with ATMs, namely cardiovascular disease and thromboembolism.[6] Compounding this, genitourinary malignancies commonly have procoagulant activity, and the prophylactic administration of ATMs in urologic oncology patients has been proposed.[7] Therefore, as ATM efficacy improves and their indications broaden, drug-associated risks become increasingly relevant.[1]

Importantly, while Wallis and colleagues reported increased bladder cancer incidence, cancer staging was not analyzed, and hence, the exact mechanism underlying increased bladder cancer remains unclear. They hypothesized that ATMs may unmask clinically silent bladder cancer by increasing bleeding, a theory which remains unproven. If true, ATM use could enable bladder cancer diagnosis at earlier stages, which would in turn argue for its accounting in standard hematuria work ups and predictive nomograms, which are currently agnostic to ATM status.[2] This simple indicator could inform the risk stratification and prioritization of further work up in patients presenting with hematuria.[8]

While Moschini et al found that patients presenting to the emergency department with gross hematuria were diagnosed with earlier stage bladder cancer when they received ATMs, their study did not include patients with microscopic hematuria or those diagnosed as outpatients, limiting the generalizability of their findings to a real-world urology practice.[1] Further understanding the effects of ATMs on bladder cancer staging is necessary. We performed a retrospective, single-institutional analysis to elucidate the potential effects of ATM use on earlier bladder cancer diagnosis.

## Materials and methods

Institutional review board approval (IRB #19D.475) was received to perform a retrospective chart review of 1052 patients who received bladder cancer diagnosis and treatment at our institution. Exclusion criteria included patients with non-urothelial histology bladder cancer or metastatic disease to the bladder. Patient demographics (age, race, ethnicity, sex, smoking status, pack years), indication for work up, CT urogram results, comorbidities (atherosclerotic cardiovascular disease (ASCVD), atrial fibrillation, cerebrovascular accident, diabetes, hypertension, hypercoagulability, and venothromboembolus history) and ATM use at diagnosis were recorded. Pathologic staging data were drawn from initial transurethral resection of bladder tumor (TURBT) as well as restaging TURBT, if performed due to incomplete initial resection or completion of initial staging.

The primary endpoint involved the effects of ATM use on bladder cancer stage at diagnosis (non-muscle invasive bladder cancer [NMIBC] vs. muscle invasive bladder cancer [MIBC]). Subgroup analyses were performed to stratify patients by individual classes of medication (aspirin, dual antiplatelet therapy, heparin, direct-acting oral anticoagulants, warfarin). Patients taking more than one ATM were excluded from subgroup analyses. Two-tailed paired t-tests and Fisher's exact tests were performed using a 95% confidence interval, with the null hypothesis that no difference in bladder cancer staging exists between ATM and non-ATM groups. Statistical analyses were performed using SPSS 28.0.1 (IBM Corp., Armonk, NY, USA).

## Results

Following chart review, 208 patients (19.8%) were excluded due to unavailability of complete diagnostic history. Ultimately, 844 patients were included in this study, including a distribution of 684 (81.0%) non-Hispanic White patients and 595 (70.5%) males. The mean age of the final cohort was 68.9 ± 11.6. Frequent comorbidities included hypertension (59.6%), smoking (69.2%), and ASCVD (22.9%).

Of these patients, 175 (20.7%) had MIBC while 669 (79.3%) had NMIBC. Within the NMIBC cohort, 160 patients received repeat TURBT but were not upstaged.

At diagnosis, 357 (42.3%) patients were taking ATMs, of whom 71 were taking two or more concurrently. Aspirin 81 mg was the most common, used by 268 of 357 (75.07%) patients, followed by clopidogrel, with 50 (14.01%) patients, and warfarin, with 31 (8.68%) patients. Smoking rates were significantly different between the

TABLE 1. **Association between ATM class and staging**

| ATM regimen | NMIBC | MIBC | p value |
|---|---|---|---|
| Any ATM | 290 | 67 | 0.23 |
| No ATM | 379 | 108 | |
| Aspirin 81 mg | 168 | 39 | 0.33 |
| No ATM | 379 | 108 | |
| DAPT | 34 | 7 | 0.56 |
| No ATM | 379 | 108 | |
| Heparin | 5 | 2 | 0.65 |
| No ATM | 379 | 108 | |
| DOAC | 19 | 3 | 0.44 |
| No ATM | 379 | 108 | |
| Warfarin | 14 | 6 | 0.42 |
| No ATM | 379 | 108 | |
| Aspirin 325 mg | 19 | 2 | 0.28 |
| No ATM | 379 | 108 | |

NMIBC = non-muscle invasive bladder cancer; MIBC = muscle invasive bladder cancer; ATM = antithrombotic medication; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant

ATM and non-ATM cohorts, as 273 (76.7%) ATM patients and 311 non-ATM patients (65.2%) smoked ($p < 0.001$).

Bladder cancer stage at diagnosis was comparable between the ATM and non-ATM patient cohorts. Within the ATM cohort, 290 (81.2%) presented with NMIBC, compared to 379 (77.8%) patients in the non-ATM cohort ($p = 0.23$). Stratification by individual classes of ATMs demonstrated no statistically significant differences in NMIBC versus MIBC staging, Table 1.

## Discussion

Our study demonstrates that although Wallis et al established that patients on blood thinners who present with hematuria are more likely to be diagnosed with genitourinary pathology, this finding does not appear to enable an earlier diagnosis of bladder cancer. This pattern seemingly holds true across subgroup analyses for individual ATM classes.

ATMs are among the most commonly prescribed medications, particularly in the cohort of adults at greatest risk for bladder cancer. These medications have been demonstrated to significantly reduce mortality from several conditions including ASCVD and venothromboembolic disorders.[3] However, considering their high rates of adverse effects, including hematuria, which can cause significant distress for patients, their effects on the genitourinary system must be considered.

There is no established link between ATM pharmacology and bladder cancer carcinogenesis, but considering our study's finding that earlier diagnosis is not enabled in ATM patients, it is difficult to conclude that ATM use is simply unmasking clinically silent bladder cancer. Further study is needed to understand how ATM use may increase bladder cancer incidence. Importantly, our comorbidities analysis demonstrated that smoking rates were higher in ATM users, which is expected given that smoking is a common risk factor underlying ATM-associated conditions and bladder cancer.

This study has limitations. Although this analysis included a large cohort of real-world patients, its retrospective, single-institutional nature confers sampling bias. Moreover, data surrounding long term outcomes, assessment of hematuria at presentation (gross versus microscopic), and low vs. high risk NMIBC presentation were missing and should be studied in future analyses.

## Conclusion

Ultimately, this analysis demonstrates that although previous literature has reported higher rates of bladder cancer diagnosis with ATM use, this did not appear to facilitate an earlier cancer diagnosis in our institutional series. Therefore, the proper incorporation of ATM use in risk stratification algorithms for hematuria work up requires further investigation. □

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