

## Do 5-alpha reductase inhibitors decrease the risk of recurrent gross hematuria in patients who have had a transurethral prostatectomy?

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### Introduction

Benign prostatic enlargement is a common cause of urinary symptoms in aging men. Some men require a transurethral prostatectomy (TURP). Previous research has shown that use of prostate-specific medication is common after TURP, despite having limited physiological basis or evidence to support their use.<sup>1</sup> 5-alpha reductase inhibitors (5ARIs) are one category of these medications and are used at some point by almost 30% of men in the first 10 years after a TURP.<sup>1</sup> In our experience, they are often prescribed for gross hematuria in patients who have had a TURP. Our objective was to determine if 5ARI use after an episode of post-TURP gross hematuria reduces the risk of further episodes of gross hematuria.

### Methods

We conducted a population-based, retrospective cohort study using data from Ontario, Canada. These datasets were linked using unique encoded identifiers and analyzed at ICES. We first identified men who had a TURP from 2003–2016 and we excluded those with a prior TURP, prostate cancer, a bladder tumor resection, or age <66 years (our previous work has further details on the study population, data sources, coding and methodology<sup>2</sup>). We then identified men who returned to the hospital/emergency room with gross hematuria at least 90 days after their TURP (to avoid identifying ongoing hematuria from the TURP<sup>3</sup>) and used the date of this initial episode of gross hematuria as the study start date. We did this to make sure all men had an episode of gross hematuria that could potentially lead to the initiation of a 5ARI. A healthcare encounter with gross hematuria was defined as a hospital, emergency room, or physi-

cian visit with a relevant ICD-10 code (R31.0), a Canadian Classification of Intervention procedure code (2PM70BA, 1PM54CATS, 1PM13BAZ9, 1PM13BAC2, 1PM52BATS, 1PM52CATS, or 1QT13), or a physician billing code (Z608, E783) related to hematuria.

Our primary exposure was the use of 5ARIs (finasteride or dutasteride) based on the Ontario Drug Benefits database.<sup>4</sup> We treated the use of 5ARIs as a time-varying exposure. This means that we accounted for men coming on and off the 5ARI, and men could have several distinct periods of 5ARI use. Continuous usage was defined as 1.5x the duration of the prescription; if another prescription was filled within this time period, the usage period was extended in a similar manner. Men were considered exposed to the 5ARI after the first 30 days of use through to the end of the period of continuous usage. We chose a 30-day wash-in period to account for the delayed effect of 5ARIs.<sup>5</sup> Each man was observed from the initial period of gross hematuria until censoring at death, emigration, treatment of prostate cancer, repeat TURP, or March 31, 2018. The primary outcome was a subsequent episode of gross hematuria (defined as above). We measured this outcome as a repeated event and considered events >7 days apart as distinct episodes of gross hematuria.

Our primary analysis (SAS version 9.4, SAS Institute, Cary, NC, U.S.) used an adjusted Anderson-Gill proportional hazards model to evaluate the association between 5ARI use and gross hematuria.<sup>6</sup> We did two post-hoc sensitivity analyses. First, we excluded men who were considered significant outliers from the model (those with  $\geq 8$  gross hematuria outcomes) to ensure the results were not driven by this small subset of the cohort. Second, we conducted an analysis that considered only the time to the first episode of recurrent gross hematuria. A p-value < 0.05 was considered significant. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

### Results

There were 9449 men who had at least one episode of gross hematuria post-TURP (representing 19% of eligible patients

who had a TURP). The median age was 80 years (Q1–Q3 75–85) and most (77%) had undergone an electrosurgical TURP (Table 1). Among this group of men post-TURP with an initial episode of gross hematuria, there were 2713 (29%) who used a 5ARI. We observed that 2752/9449 (29.1%) men had at least one additional future healthcare encounter for gross hematuria (1695 [61.6%] had only a single event, 567 [20.6%] had two events, and 490 [17.8%] had three or more events).

Our primary adjusted analysis showed that 5ARI users had an increased rate of healthcare encounters for gross hematuria compared to non-5ARI users (event rate 6.63 vs. 5.70 per 10 000 person-years, respectively, adjusted hazard ratio [HR] 1.22,  $p < 0.01$ ). However, two sensitivity analyses suggested no significant association between 5ARI use and future episodes of gross hematuria (Table 2). We explored the reason why there might have been an increased risk associated with 5ARIs (contrary to our hypothesis) and found men who used 5ARIs were significantly more likely to undergo a second TURP, which we considered a censoring event (adjusted HR 1.54, 95% confidence interval 1.36–1.74,  $p < 0.01$ ).

## Discussion

We did not find that 5ARI use among men with an episode of gross hematuria post-TURP reduced the rate of repeat episodes of gross hematuria requiring medical attention compared to non-5ARI users. The possible increased risk of gross hematuria with use of 5ARIs was likely driven by a small number of men with a high number of repeated episodes of gross hematuria, and our sensitivity analysis did not support a significant association between 5ARI and gross

hematuria in this population. TURP (a competing treatment for gross hematuria) was more common in 5ARI users and this suggests that the true HR from the primary analysis is  $< 1.22$  (closer to a null association).<sup>6</sup> The use of 5ARIs after TURP is common, however, their efficacy is not proven. A single randomized controlled trial did not show any benefit with 5ARIs in terms of reducing the rate of repeat TURP or bleeding, or improving voiding.<sup>7</sup> Chart review studies have suggested that risk factors for early postoperative gross hematuria following endoscopic prostate resection or vaporization may include large prostate size, use of anticoagulation, and younger age, and the benefit of 5ARIs during this initial period is inconsistent.<sup>8,9</sup> We feel that the evidence for gross hematuria reduction in operation-naïve prostates<sup>10</sup> and during TURP<sup>5</sup> should not be automatically extrapolated to the post-TURP period. Given the lack of evidence supporting the use of 5ARIs after TURP, and their potential adverse effects,<sup>11</sup> their use should be further evaluated in clinical trials specific to this clinical scenario.

Limitations of our work include the fact that we could not measure all relevant baseline characteristics (such as volume of prostate or resected tissue), and we relied on filled prescriptions as a surrogate of medication use. Administrative data could only identify men who sought medical care for gross hematuria, which likely skewed towards more severe cases of gross hematuria. We could not identify the clinical reason why 5ARIs were prescribed. Finally, residual confounding may be present, as the use of 5ARI after TURP is likely not a random process.

**Competing interests:** The authors report no competing personal or financial interests related to this work.

**Table 1. Baseline characteristics of men who had at least one recurrent episode of gross hematuria after TURP**

	No 5ARI use after the initial episode of gross hematuria	5ARI use after the initial episode of gross hematuria	p
	n=6736	n=2713	
Age, median (Q1–Q3)	80 (75–85)	80 (75–85)	0.251
<b>Characteristics at the time of the TURP</b>			
TURP at an academic hospital	788 (11.7%)	399 (14.7%)	<0.001
Gross hematuria in year prior to TURP	2,217 (32.9%)	918 (33.8%)	0.388
Type of TURP Procedure			<0.001
Electrical	5294 (78.6%)	2028 (74.8%)	
Laser	670 (10.0%)	378 (13.8%)	
Unknown	772 (11.5%)	307 (11.3%)	
Cystolithopaxy with TURP	606 (9.0%)	293 (10.8%)	0.007
Diabetes	1496 (22.2%)	592 (21.8%)	0.681
5ARI use in the 6 months prior to TURP	1580 (23.5%)	1190 (43.9%)	<0.001
<b>Characteristics at the time of the first episode of gross hematuria</b>			
5ARI use in the 3 months prior gross hematuria	115 (1.7%)	1086 (40.0%)	<0.001
Time since initial TURP, median years, (Q1–Q3)	3 (1–5)	3 (1–6)	0.009
Anticoagulant use in the 3 months prior gross hematuria	148 (2.2%)	60 (2.2%)	0.966

5ARI: 5-alpha reductase inhibitors; TURP: transurethral prostatectomy.

**Table 2. Results of the primary multivariable model and two sensitivity analysis examining the probability of repeated episodes of gross hematuria**

	5ARI use	p
Primary analysis*	HR 1.22 (1.05–1.43)	0.009
Sensitivity analysis*		
1. Primary analysis with exclusion of 59 (representing 2.14%) men in the 99.5 percentile of gross hematuria episodes ( $\geq 8$ during followup)**	HR 1.12 (1.00–1.25)	0.051
2. Primary analysis considering only the time to first episode of gross hematuria	HR 1.04 (0.93–1.17)	0.457

The reference category for all analyses is men not using 5ARI medications. \*All analyses were adjusted for the following covariates: 5ARI exposure, age, fiscal year, academic hospital, gross hematuria in year prior to TURP, type of TURP, cystolithopaxy with TURP, diabetes, 5ARI use in the 6 months prior to TURP, 5ARI use in the 3 months prior to gross hematuria, time since initial TURP, anticoagulant use in the 3 months prior gross hematuria.

\*\*A total of 59 men experienced  $\geq 8$  episodes of gross hematuria; 45.8% and 54.2% were removed from the analysis in the 5ARI and non-5ARI groups, respectively, for this sensitivity analysis. 5ARI: 5 alpha reductase inhibitors; HR: hazard ratio; TURP: transurethral prostatectomy.

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