The association of statin subgroups with lower urinary tract symptoms following a prostate biopsy

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Abstract

Introduction: This was a secondary analysis aiming to assess whether hydrophilic or hydrophobic statins have a differential effect on urinary retention (UR) and lower urinary tract

symptoms (LUTS) in men following a prostate biopsy (PB), who were at risk for prostate cancer development.
Methods: This was a population-based cohort study with data incorporated from the Institute for Clinical and Evaluative Sciences database to identify all Ontarian men aged 66 and above with a history of a single negative PB between 1994 and 2016, with no drug prescription history of any of several putative chemopreventative medications (statins, proton pump inhibitors, five-alpha-reductase inhibitors, and alpha-blockers). Multivariable Cox regression models with time-dependent covariates were used to assess the association of hydrophilic and hydrophobic statins with UR and LUTS within 30 days of a PB. All models were adjusted for other known putative chemopreventive medications, age, rurality, pharmacologically treated diabetes, comorbidity score, and study inclusion year.
Results: Overall, 21 512 men were included, with a median followup time of 9.4 years (interquartile range [IQR] 5.4–13.4 years). Hydrophobic and hydrophilic statins were initiated by 30.7% and 19.6% of men, respectively, after the first negative PB. UR and LUTS were experienced by 2.2% and 10% of men, respectively. Cox models demonstrated hydrophilic statins were associated with a lower risk of UR (hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.38–0.83, p=0.0038) and LUTS (HR 0.86, 95% CI 0.76–0.98, p=0.022), while no such association was shown for hydrophobic statins.
Conclusions: Initiation of hydrophilic statins in men older than 66 appears to be inversely associated with the risk of UR and LUTS within 30 days of a PB.

Introduction

Transrectal ultrasound-guided prostate biopsy (PB) is still considered the gold standard approach for prostate cancer (PCa) diagnosis[1]. PB is one of the most commonly performed urological procedures, with over one million procedures performed yearly in the United States[2]. Despite being generally considered a relatively low-risk outpatient procedure, there are still considerable complications, including hematuria (10-84%)[1,2], hematochezia (2.2-36.8%)[1,3], hematospermia (1.1-93%)[4], febrile urinary tract infection (3.5%)[5], acute urinary retention (UR; 0.2-1.7%)[4,6], lower urinary tract symptoms (LUTS; 6-25%)[7], erectile dysfunction[8], vasovagal response[1,2], pain and anxiety[9], and even death (0.09% 30-day mortality rate, most commonly due to septic shock)[10].

Common risk factors for UR following PB include large prostate volume, high ratio of transitional zone volume to total prostate volume, and high International Prostate Symptom Score (IPSS)[11]. In most cases, the retention is self-limiting and urinary catheterization is recommended for 5 to 7 days.

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase [HMGCoAR] inhibitors) are predominantly used for lipid profile improvement and reduction of cardiovascular morbidity and mortality[12]. Statins can be divided into two: hydrophilic (pravastatin and rosuvastatin) and hydrophobic (simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin) statins[13]. Both subgroups have similar cholesterol reduction effect but exhibit different pleiotropic effects, reflecting their distinct lipophilicity. This, in turn, affects their pharmacokinetic and metabolic attributes. Currently, there are no formal recommendation to prefer one statin over the other, as long as known drug interactions with specific statins are avoided.

Interestingly, statins have been shown to be associated with a 6.5-7 year delay in the onset of moderate/severe LUTS or benign prostatic hyperplasia (BPH)[14]. Moreover, among men >60 years, statins were shown to have a significant inverse association with LUTS severity (odds ratio=0.15, 95% CI: 0.05-0.44)[15]. There are several suggested theoretical explanations for this unique association, including an anti-ischemic[16], anti-inflammatory[17], and anti-angiogenic[18] effects caused by statins.

Our original study was to investigate the role of different statin subgroups in prostate cancer (PCa) chemoprevention in men who have had a single negative PB. This recently published analysis showed a beneficial role specifically for hydrophilic statins, but not for hydrophobic statins[19]. In this secondary study, we aimed to analyze whether any difference exists between hydrophilic and hydrophobic statins with UR rates and LUTS within 30 days of a PB, while adjusting for other commonly prescribed medications and baseline clinical factors.

Methods

This study was approved by the ethics board committee of the University of Toronto and the University Health Network. The study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines[20] and Reporting of Studies Conducted Using Observational Routinely-Collected Health Data statement[21]. We assembled a cohort of men aged 66 or above in Ontario, Canada, with a history of a single negative PB and no prior use of any of several various putative PCa chemopreventative medications as part of our original analysis[19]. As previously mentioned, we utilized the administrative data housed at the Institute for Clinical and Evaluative Sciences (ICES) with the primary intent of assessing the extent of the chemopreventative effect of these medications in PCa[19]. However, for this specific secondary study, our goal was to assess the associations of the various subgroups of statins with UR and LUTS within 30 days of a PB.

In the province of Ontario, the Ontario Health Insurance Plan (OHIP) is the only government-funded health insurance system that reimburses all essential medical care. This enables capture and access to the entire adult population and their anonymized data. Additionally, in Ontario, medication prescription is freely available to everyone 65 years and older through the Ontario Drug Benefit (ODB) program. Consequently, this allows for the accurate capture of all provided prescriptions in the analyzed population.

Data sources

Data were acquired from the datasets housed at ICES[22] and detailed in supplemental Table 1. The retrieved data contained demographic, baseline comorbidity, medication prescription, and data on UR and LUTS within 30 days of a PB. The data of each patient were linkable using a unique encoded identifier.

Study design and participants

For this secondary analysis, we included all men in the province of Ontario with a minimum age of 66 years, who underwent one single negative transrectal ultrasound (TRUS) guided PB between January 1st, 1994, and September 30th, 2016. The age cut-off of 66 years was used to enable a one-year look-back period, confirming that no drug prescription of any of the analyzed putative chemopreventative medications was given during a minimum period of one year, and all men analyzed were definitively medication-naïve at inclusion. For the purpose of identification of all relevant patients, OHIP billing codes for TRUS-guided PB, and the specific Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures codes were used to make sure no record of PCa diagnosis, nor receipt of PCa-specific treatment existed within the three months after the first PB. The codes used for this study are detailed in Supplemental Table 2. Men with a history of a previous negative PB were chosen as part of a screening method to include a 'healthier' population since they were seen fit enough to undergo a PB. A look-back window of a minimum of three years, from January 1991 until cohort entry (as data were not available before that), was used to include only men with a single negative PB and no PCa diagnosis; and to capture the comorbidity score of each man. For this study, the index date was defined as 90 days following the date of the first negative PB. Patients were followed from the index date until one of four possible outcomes: 1) Death, 2) Last health services contact in Ontario, 3) Becoming OHIP ineligible, or 4) End of the study period (September 30th, 2016).

Study outcomes

Our primary and secondary outcomes were transurethral catheter insertion due to UR and experiencing LUTS, manifested as either frequency, urgency, or difficulty emptying the bladder, within 30 days of a PB, respectively, examined as a time to event outcome.

Study variables

Data on several commonly prescribed medications were acquired as part of the initial analysis and publication[19]. These included statins divided into hydrophilic and hydrophobic statins, five-alpha-reductase inhibitors (5ARIs), alpha-blockers, and proton pump inhibitors. Of note, glaucoma eye drops served as a negative tracer drug and was incorporated into all models.

Other variables acquired included patient age (categorized as 66-69, 70-74, 75-79, 80-84, and 85 years and above due to registry security issues), rurality index (continuous variable, with a higher number representing residence in a more rural area)[23], year of study inclusion (index year), comorbidity status quantified with the Collapsed Ambulatory Diagnostic Groups (ADG) score (a continuous comorbidity variable derived from the Johns Hopkins Adjusted Clinical Groups System)[24], and pharmacologically treated diabetes (binary variable indicating whether a man had diabetes treated with either metformin, sulfonylurea, thiazolidinediones, or insulin).

Statistical analyses

Continuous variables were described using means and standard deviations (SD); categorical variables were characterized using proportions. We assessed the association between medication exposure and the analyzed outcomes. Multivariable Cox proportional hazard regression models with time-dependent exposure were used for each cause-specific hazard as these are best suited to deal with time-dependent covariates in such an analysis[25]. To obtain information on general and cumulative medication exposure, the exposure to each medication was specified as a time-dependent variable (ever vs. never exposure at any time point during the follow-up, and the effect of the cumulative exposure of each medication per six-months of use). All models were also adjusted for *a priori* selected covariates, using the values at study onset. These included age category, diabetes, and the following continuous variables with log-linear effects: rurality index (0-100), index year (1994-2016), and ADG comorbidity score. The proportionality and log-linearity assumptions underlying the multivariable models were assessed using residual-based diagnostics, without any evidence of violations. All statistical tests were two-tailed with a p-value of less than 0.05 considered significant. All statistical analyses were performed using R software version 3.3.1.

Results

Between 1994 and 2016, 21,512 Ontarian men 66 years or older with a history of a single negative PB and no previous treatment with any of the analyzed putative chemopreventative medications were identified. The study's consort diagram is shown in Supplemental Figure 1. The median follow-up time (interquartile range [IQR]) was 9.4 years (8 years). Table 1 depicts basic demographic data of all men at study inclusion stratified by age category. Supplemental Figure 2 depicts the use of commonly prescribed medications among study participants, stratified by duration of use. The most used medications included proton pump inhibitors (PPIs, 51.1%), alpha-blockers (39.5%), hydrophobic statins (30.7%), and hydrophilic statins (19.6%). Figure 1 shows the number of additional biopsies that men underwent during the 22-year study period. A total of 35.1% and 11.8% of men underwent at least one and two additional PBs, respectively. In the 30 days following an additional PB, 466 patients (2.2%) experienced UR requiring catheterization, and 2,159 patients (10%) experienced LUTS (Figure 2).

Multivariable Cox proportional hazard modeling demonstrate that any use of hydrophilic statins (HR 0.561, 95% CI0.380-0.830, p=0.0038) was associated with a decreased risk of UR while the use of hydrophobic statins did not demonstrate any such association (HR 1.23, 95% CI 0.972-1.579, p=0.082) (Table 2). Additional demographic characteristics and medication use were associated with the risk of UR: pharmacologically treated diabetes (HR 1.980, 95% CI

1.443-2.716, p<0.0001), increased number of previous biopsies (HR 1.170, 95% CI 1.055-1.297, p=0.0027), any use of alpha-blockers (HR 1.800, 95% CI 1.434-2.263, p<0.0001), and study index year (HR 0.966, 95% CI 0.945-0.989, p=0.0035).

Multivariable Cox proportional hazards modeling showed that any use and every six months cumulative use of hydrophilic statins (HR 0.859, 95% CI 0.755-0.979, p=0.022), and (HR=0.977, 95% CI 0.960-0.995, p=0.016), respectively, were associated with a decreased risk of LUTS. In contrast, hydrophobic statins did not demonstrate such association (HR 0.998, 95% CI 0.902-1.105, p=0.980). Additional demographic characteristics and medication use were associated with the risk of LUTS: Increasing age (80-84 years) compared to age 66-69 years (HR 1.458, 95% CI 1.184-1.796, p=0.0003), study index year (HR 1.066, 95% CI 1.055-1.077, p<0.0001), any treatment and every six months cumulative use of alpha-blockers (HR 1.979, 95% CI 1.800-2.176, p<0.0001), and (HR 1.048, 95% CI 1.038-1.058, p<0.0001), respectively, any use and every six months cumulative use of 5ARIS ((HR 0.800, 95% CI 0.705-0.907, p=0.0005), and (HR 0.939, 95% CI 0.920-0.959, p<0.0001)), respectively.

Lastly, no associations were noted between all evaluated outcomes and the tracer medication (glaucoma eye drops).

Discussion

Our study showed that 35.1% of Ontarian men aged 66 or above who underwent a single negative PB and had no prior use of the analyzed medications had at least one additional PB during a 20-year follow-up period. The UR and LUTS rates within 30 days of a PB were 2.2%, and 10%, respectively. Incident use of hydrophilic statins was associated with a decreased likelihood of UR and LUTS within 30 days of an additional PB, while no such association was seen with hydrophobic statins. As expected, 5ARIs were associated with a decreased likelihood of LUTS, while Alpha-blockers were associated with an increased rate of UR and LUTS. Lastly, an increased number of biopsies was associated with a higher likelihood of UR.

The rate of UR following one single PB is reported to be 0.2-1.7%[4,6]. However, in our reported population, 35% of men had at least two PBs, and 11.8% underwent three PBs or more, potentially explaining the higher rate of UR observed in our study (2.2%). Furthermore, aging is associated with an increased risk of UR[26]. Moreover, almost 40% and 23% of our cohort were treated with alpha-blockers and 5ARIs, respectively, suggesting that they were already experiencing LUTS and at an increased risk of developing UR. It has been shown that 12% and 8% of men undergoing PB experience mild and moderate LUTS one week following PB, respectively[27]. This is very similar to our reported result of a 10% incidence of LUTS.

There are contradicting data on the association of statins with LUTS and BPH. In a randomized double-blinded, placebo-controlled trial, atorvastatin, a hydrophobic statin, was not shown to improve LUTS over a 6-month period[28]. Additionally, when compared to finasteride (a 5ARI) alone, the combination of lovastatin (another hydrophobic statin), with finasteride was not shown to reduce LUTS more, or further decrease prostate volume or PSA, after four months of treatment[29]. Contrasting these findings, there are several studies showing a significant protective association between statins and LUTS. A randomized prospective study randomizing 135 BPH patients with metabolic syndrome to receive statins or placebo for 12 months showed that statins resulted in reduced IPSS scores and prostate volumes, compared to placebo-treated patients[30]. In a large retrospective analysis, statin use was associated with 6.5-7 years delay in new-onset of LUTS and BPH[14]. A study from the Boston Area Community Health (BACH) Survey[15] found that in men >60 years, statins demonstrated a significant inverse association with LUTS[15], corroborating our own findings. Moreover, a recently published meta-analysis, including five randomized controlled studies and six cohort studies, analyzing over 49,000 patients, suggested that statins can reduce BPH risk in patients >60 years (Odds ratio=0.35, 95% CI 0.22-0.55, P<0.0001)[31].

The etiology of this suggested beneficial association of statins with LUTS is unknown. There are however, several possible suggested mechanisms, which include: 1) reduced ischemia, 2) anti-inflammatory effect, 3) anti-angiogenesis and 4) PSA decrease. Bladder outlet obstruction (BOO) resulting from BPH can trigger ischemia during detrusor contraction[16]. This eventually leads to impaired contractility, and worsening LUTS [32]. It has been suggested that by reducing atherosclerosis in bladder blood vessels, statins reduce the ischemic impact of BOO, preventing LUTS development[15]. IL-6 has been shown to be elevated in patients with metabolic syndrome and men with BPH[33], suggesting that metabolic syndrome might be contributing to the inflammation seen in BPH resulting in LUTS. Statins were demonstrated to elicit anti-inflammatory effects by decreasing IL-6 levels[17] and significantly reducing the proliferation rate of prostate cells[34], perhaps causing less bothersome LUTS. Moreover, using data from the REDUCE trial, Allott et al. reported that statin use was associated with decreased histological indices of prostate inflammation, specifically among men with a negative PB, identical to our own study population[35]. Statins were also shown to exhibit anti-angiogenesis effects and inhibit capillary formation, reducing the release of vascular endothelial growth factor, and improving LUTS[18]. Lastly, statins were noted to be associated with reduced PSA levels[36]. Since low PSA is correlated with prostate size, it has been suggested that statins might be associated with lower prostate volumes, leading to decreased LUTS[14].

The varying lipophilicity of hydrophobic and hydrophilic statins is responsible for their different pleiotropic effects[37]. The variable lipophilicity changes their solubility and localization, ultimately resulting in a considerable difference in metabolic effects[38]. Hydrophilic statins are hepato-specific, using carrier-mediated mechanisms for hepatic cell uptake[39]. Some of these carriers are extra-hepatic, found in the prostate, enabling uptake[40]. In contrast, hydrophobic statins passively diffuse into various cells and are widely distributed. A possible explanation for the contradicting published findings could reflect the fact that past studies analyzed statins as one single group[29] or evaluated only hydrophobic statins[28,29]. Hydrophobic statins have exhibited no protective association in our study. Perhaps the potential mechanisms previously discussed, resulting in a favorable association with LUTS, are uniquely relevant to hydrophilic rather than to hydrophobic statins.

Our study's validity is demonstrated by the clear associations shown between use of alpha-blockers and 5ARIs with LUTS, the association between the cumulative number of PBs and the risk of UR, and the fact that no associations were noted between all evaluated outcomes and the tracer medication (glaucoma eye drops).

The strengths of our study lie in its large population-level cohort of men treated in the same health system over a relatively long time. All men were medication-naïve at study inclusion and initiated treatment with the analyzed medications only during the study period. Additionally, this is the only study specifically assessing the association of each statin subgroup with UR and LUTS. Nonetheless, some important limitations are noteworthy. First, is the inherent selection bias of the analyzed population, consisting of men at risk for PCa with a history of a single negative PB, prone to undergo more PBs, have more severe LUTS, and followed more intensely by urologists. Second, are the potential inaccuracies embedded in health administrative databases like those used in this study, potentially increasing the likelihood of discovering spurious associations. Third, our data was limited to men older than 66 years, as data on younger men were not available. Fourth, the diagnosis of LUTS was not quantified and standardized in a measurable manner and was based on physician reported diagnosis. Fifth, clinically important information, including race, PSA levels, prostate volume, bladder function, PB details, prebiopsy IPSS, LUTS, and UR history, were not available. Sixth, we did not account for other potential common medications in this unique population, including anticholinergics, beta-3 agonists, phosphodiesterase type 5 inhibitors, and over the counter prostate supplements, which could have had some effect. Seventh, diabetic patients were defined as only those who were pharmacologically treated. Lastly, unaccounted residual confounding is potentially present in these types of studies.

Conclusions

The initiation of hydrophilic statins in men > 66 years at risk for PCa appears to be inversely associated with the risk of UR and LUTS within 30 days of a PB. The mechanism by which hydrophilic and not hydrophobic statins harbor this association needs further research. Upon validation of these findings in other large cohorts, men treated with hydrophilic statins may gain additional benefits, irrespective of the cholesterol-lowering effect, as this may provide some protective effect of LUTS and UR, especially if they undergo a PB.

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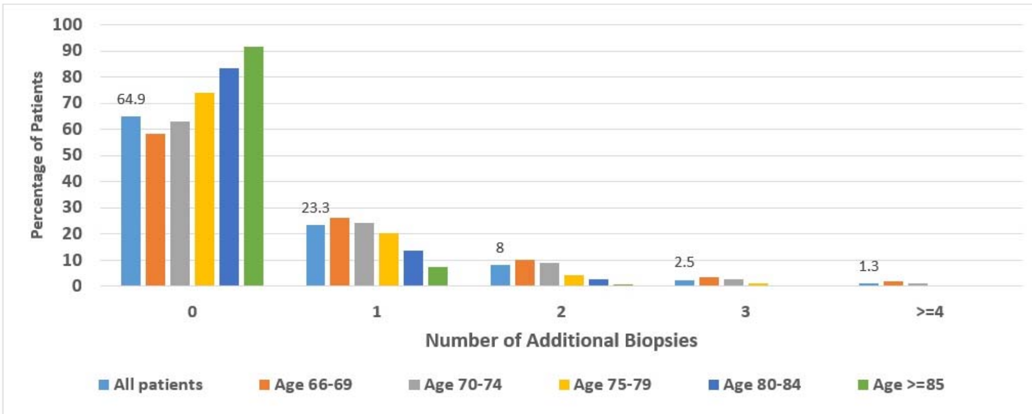
Figure and Tables

Fig. 1. Additional prostate biopsies stratified by age.



Number of Additional Biopsies (%)	All patients	66-69 years	70-74 years	75-79 years	80-84 years	>=85 years
0	13956 (64.9)	4940 (58.2)	4728 (63.1)	2751 (73.9)	1111 (83.2)	426 (91.6)
1	5008 (23.3)	2219 (26.1)	1816 (24.2)	754 (20.3)	184 (13.8)	35 (7.5)
2	1726 (8.0)	851 (10)	675 (9)	162 (4.4)	35 (2.6)	3 (0.6)
3	542 (2.5)	304 (3.6)	193 (2.6)	40 (1.1)	4 (0.3)	1 (0.2)
4	187 (0.9)	114 (1.3)	60 (0.8)	11 (0.3)	2 (0.1)	0
5	55 (0.3)	37 (0.4)	16 (0.2)	2 (0.1)	0	0
6	24 (0.1)	17 (0.2)	7 (0.1)	0	0	0
7	9 (0)	6 (0.1)	2 (0)	1 (0)	0	0
8	5 (0)	4 (0)	0	1 (0)	0	0

Fig. 2. Percentage of urinary retention and lower urinary tract symptoms within 30 days of the prostate biopsy among men stratified by age.

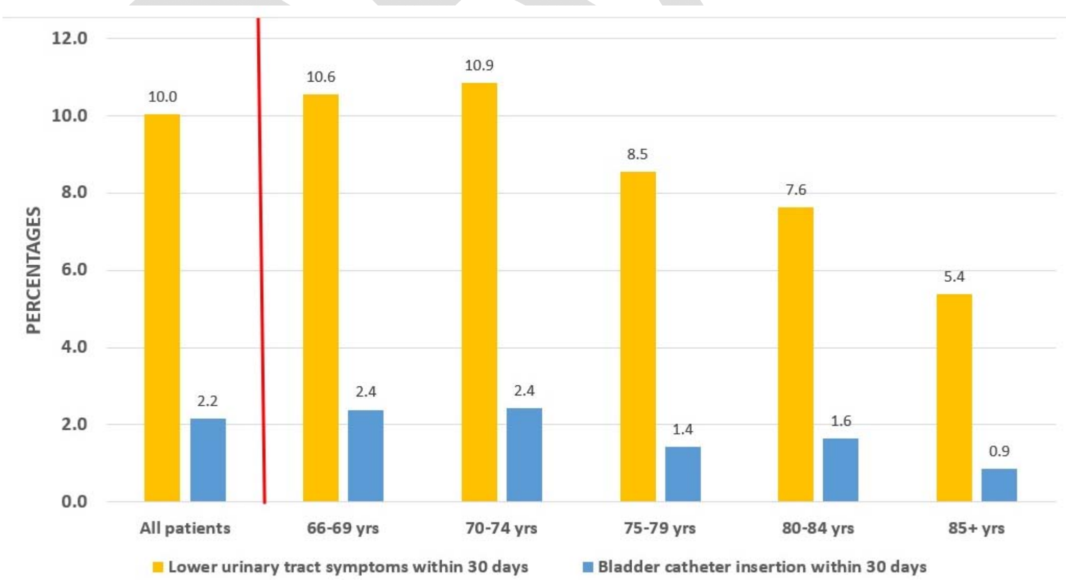


Table 1. Basic demographic characteristics of all patients						
	All patients	**Age 66–69**	**Age 70–74**	**Age 75–79**	**Age 80–84**	**Age ≥85**
Number of men (%)	21 512 (100%)	8492 (39.5%)	7497 (34.8%)	3722 (17.3%)	1336 (6.2%)	465 (2.2%)
Time period, n (%)						
1994–2000	12131 (56.4%)	4281 (50.4%)	4317 (57.6%)	2360 (63.4%)	863 (64.6%)	310 (66.7%)
2001–2007	6634 (30.8%)	2777 (32.7%)	2316 (30.9%)	1037 (27.9%)	392 (29.3%)	112 (24.1%)
2008–2014	2747 (12.8%)	1434 (16.9%)	864 (11.5%)	325 (8.7%)	81 (6.1%)	43 (9.2%)
Mean ADG score, (SD)	18.97 (11.62)	16.85 (10.9)	18.66 (11.28)	21.44 (11.97)	24.33 (12.09)	27.49 (12.95)
Patients with pharmacologically treated diabetes, n (%)	2331 (10.8%)	1051 (12.4%)	833 (11.1%)	345 (9.3%)	81 (6.1%)	21 (4.5%)
Mean rurality index (SD)	11.63 (17.43)	11.66 (17.38)	11.78 (17.72)	11.66 (17.34)	11.05 (16.81)	10.06 (16.09)
Income quintile, n (%)						
1	3439 (16%)	1260 (14.8%)	1157 (15.4%)	686 (18.4%)	242 (18.1%)	94 (20.2%)
2	4167 (19.4%)	1570 (18.5%)	1470 (19.6%)	751 (20.2%)	277 (20.7%)	99 (21.3%)
3	4289 (19.9%)	1655 (19.5%)	1498 (20.0%)	759 (20.4%)	283 (21.2%)	94 (20.2%)
4	4356 (20.2%)	1807 (21.3%)	1500 (20.0%)	706 (19.0%)	260 (19.5%)	83 (17.8%)
5	5164 (24%)	2165 (25.5%)	1833 (24.4%)	805 (21.6%)	268 (20.1%)	93 (20.0%)
Not available	97 (0.5%)	35 (0.4%)	39 (0.5%)	15 (0.4%)	6 (0.4%)	2 (0.4%)

ADG: Johns Hopkins Aggregated Diagnosis Groups. SD: standard deviation.

Table 2. Cox proportional hazards multivariable regression model demonstrating the association with the risk of transurethral catheter insertion within 30 days of a prostate biopsy with medications modeled as ever vs. never and cumulative 6 months usage

	Medications modeled as ever vs. never		**Medications modeled using cumulative 6 months use intervals**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Age category (reference 66-69 years)				
70–74 years	1.045 (0.854–1.278)	0.669	1.057 (0.864–1.292)	0.587
75–79 years	0.728 (0.537–0.987)	0.041	0.731 (0.539–0.991)	0.04
80–84 years	1.039 (0.664–1.620)	0.867	1.040 (0.669–1.636)	0.839
≥85 years	0.700 (0.262–1.910)	0.499	0.715 (0.264–1.936)	0.51
ADG score (continuous variable)	1.003 (0.994–1.011)	0.471	1.003 (0.994–1.011)	0.477
Rurality index (continuous variable)	0.991 (0.985–0.997)	0.006	0.991 (0.985–0.997)	0.0046
Index year (continuous variable)	0.966 (0.945–0.989)	0.0035	0.968 (0.947–0.989)	0.0039
Diabetes (yes vs. no)	1.980 (1.443–2.716)	<0.0001	1.980 (1.450–2.720)	<0.0001
Cumulative num. of biopsies (continuous variable)	1.170 (1.055–1.297)	0.0027	1.180 (1.069–1.312)	0.0012
Glaucoma eye drops	0.817 (0.485–1.377)	0.449	0.876 (0.701–1.094)	0.243
5ARI	0.880 (0.633–1.22)	0.452	0.976 (0.925–1.030)	0.39
Alpha-blockers	1.800 (1.434–2.263)	<0.0001	1.017 (0.988–1.048)	0.234
Hydrophobic statins	1.23 (0.972–1.579)	0.082	1.016 (0.993–1.040)	0.151
Hydrophilic statins	0.561 (0.380–0.830)	0.0038	0.952 (0.898–1.008)	0.0966
PPIs	0.952 (0.864–1.05)	0.330	0.977 (0.959–0.997)	0.024

ADG: Johns Hopkins Aggregated Diagnosis Groups; 5ARIs: 5-alpha reductase inhibitors; CI: confidence interval; HR: hazard ratio; PPIs: proton pump inhibitors.

Table 3. Cox proportional hazards multivariable regression model demonstrating the associations with developing lower urinary tract symptoms within 30 days of a prostate biopsy with medications modeled as ever vs. never and cumulative 6 months usage

	Medications modeled as ever vs. never		**Medications modeled using cumulative 6 months use intervals**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Age category (reference 66–69 years)				
70–74 years	1.112 (1.011–1.224)	0.029	1.126 (1.023–1.239)	0.014
75–79 years	1.136 (0.997–1.293)	0.054	1.144 (1.005–1.303)	0.041
80–84 years	1.458 (1.184–1.796)	0.0003	1.476 (1.1989–1.817)	0.0002
≥85 years	1.660 (1.111–2.479)	0.013	1.695 (1.135–2.531)	0.009
ADG score (continuous variable)	1.001 (0.997–1.005)	0.390	1.001 (0.997–1.005)	0.411
Rurality index (continuous variable)	1.003 (1.0009–1.005)	0.006	1.003 (1.0007–1.005)	0.010
Index year (continuous variable)	1.066 (1.055–1.077)	<0.0001	1.069 (1.058–1.080)	<0.0001
Diabetes (yes vs. no)	1.167 (1.003–1.358)	0.044	1.185 (1.018–1.378)	0.027
Cumulative num. of biopsies (continuous variable)	0.972 (0.924–1.023)	0.283	0.989 (0.941–1.040)	0.687
Glaucoma eye drops	1.012 (0.839–1.219)	0.900	1.025 (0.980–1.071)	0.275
5ARI	0.800 (0.705–0.907)	0.0005	0.939 (0.920–0.959)	<0.0001
Alpha-blockers	1.979 (1.800–2.176)	<0.0001	1.048 (1.038–1.058)	<0.0001
Hydrophobic statins	0.998 (0.902–1.105)	0.980	1.0001 (0.990–1.009)	0.983
Hydrophilic statins	0.859 (0.755–0.979)	0.022	0.977 (0.960–0.995)	0.016
PPIs	0.896 (0.804–0.998)	0.046	0.994 (0.978–1.010)	0.509

ADG: Johns Hopkins Aggregated Diagnosis Groups; 5ARIs: 5-alpha reductase inhibitors; CI: confidence interval; HR: hazard ratio; PPIs: proton pump inhibitors.