**THE SUGGESTED BENEFICIAL ASSOCATION OF HYDROPHILIC STATINS WITH LOWER URINARY TRACT SYMPTOMS FOLLOWING A PROSTATE BIOPSY**

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**Abstract**

***Introduction***

Transrectal ultrasound-guided prostate biopsy (PB) is a common urological procedure used for prostate cancer (PCa) diagnosis. Potential complications include urinary retention (UR) and lower urinary tract symptoms (LUTS). Statins can be divided into hydrophilic and hydrophobic statins, and they have been associated with decreased LUTS. We aimed to analyze the association of statin subgroups on UR and LUTS in men at risk for prostate cancer (PCa) following a PB.

***Materials & methods***

Data were incorporated from the Institute for Clinical and Evaluative Sciences to identify all medication-naive men aged 66 and above with a history of a single negative PB between 1994 and 2016. Multivariable Cox regression models with time-dependent covariates were used to assess the association of both statin subgroups on UR and LUTS within 30 days of a PB, and of undergoing transurethral resection of prostate (TURP). All modes were adjusted for other commonly prescribed medications, age, rurality, diabetes, comorbidity score, and study inclusion year.

***Results***

Overall, 21,512 men were included, with a median follow-up time of 9.4 years (IQR 8 years). Hydrophobic and hydrophilic statin was initiated by 30.7% and 19.6% of men during the study, respectively. UR and LUTS within 30 days of the PB were experienced by 2.2% and 10% of men, respectively. The TURP rate was 18.5%. Multivariable Cox models demonstrated that a lower rate of UR and LUTS were associated with hydrophilic statin use (HR 0.561, 95% CI0.380-0.830) and (HR 0.859, 95% CI 0.755-0.979), respectively. No similar association with hydrophobic statins was evident.

***Conclusion***

Hydrophilic statin initiated by men older than 66 at risk for PCa appears to be inversely associated with the hazard of UR and LUTS within 30 days of a PB. Pending validation of these findings, hydrophilic and not hydrophobic statins should be considered as the drug of choice in men at risk for PCa.

**Introduction**

Transrectal ultrasound-guided prostate biopsy (PB) is still considered the gold standard approach for prostate cancer (PCa) diagnosis[1](#_ENREF_1). PB is one of the most commonly performed urological procedures, with over one million procedures performed yearly in the US[2](#_ENREF_2). Despite being generally considered a relatively low-risk outpatient procedure, there are still considerable complications which include hematuria (10-84%)[1-5](#_ENREF_1), rectal bleeding (2.2-36.8%)[1](#_ENREF_1),[6](#_ENREF_6), hematospermia (1.1-93%)[7](#_ENREF_7), febrile urinary tract infection (3.5%), with 3.1% requiring hospitalization[8](#_ENREF_8), acute urinary retention (UR) (0.2-1.7%)[5](#_ENREF_5),[7](#_ENREF_7),[9](#_ENREF_9), lower urinary tract symptoms (LUTS) (6-25%)[10](#_ENREF_10),[11](#_ENREF_11), erectile dysfunction[12](#_ENREF_12), vasovagal response[1](#_ENREF_1),[2](#_ENREF_2), pain and anxiety[13](#_ENREF_13), and even death (0.09% 30-day mortality rate, most commonly due to septic shock)[14](#_ENREF_14).

UR requiring temporary bladder catheterization can occur in up to 1% of men undergoing transrectal PB[9](#_ENREF_9),[15](#_ENREF_15),[16](#_ENREF_16). Common risk factors include increased prostate volume, the ratio of transition zone volume to total prostate volume, and a higher International Prostate Symptom Score (IPSS)[16](#_ENREF_16). In most cases, the retention is self-limiting, and urinary catheterization is recommended for approximately 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[17](#_ENREF_17). Interestingly, statin use has also been shown to be associated with a 6.5-7 year delay in the onset of moderate/severe LUTS or benign prostatic hyperplasia (BPH)[18](#_ENREF_18). Moreover, among older men (>60 years), statin use was shown to have a significant inverse association with the rate of LUTS (odds ratio=0.15, 95% CI: 0.05-0.44)[19](#_ENREF_19).

Statins can generally be divided into two subgroups: hydrophilic (pravastatin and rosuvastatin) and hydrophobic (simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin) statins[20](#_ENREF_20). Both subgroups have similar cholesterol reduction effect, but harbor different pleiotropic effects, caused by their differing levels of lipophilicity. This, in turn, affects their pharmacokinetic attributes, leading to various metabolic changes.

We aimed to analyze the short-term association of the different statin subgroups with UR and LUTS rates within 30 days of a PB, and their association with undergoing transurethral resection of prostate adenoma (TURP) procedure, while adjusting for other commonly prescribed medications. This was a secondary analysis, part of our primary study of deciphering the associations of various putative chemopreventative medications with PCa diagnosis and PCa specific death (currently in review).

**Methods**

Approval by the ethics board committee of the University of Toronto and the University Health Network was given for this study. The study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines[21](#_ENREF_21) and Reporting of Studies Conducted Using Observational Routinely-Collected Health Data statement[22](#_ENREF_22). We originally utilized administrative data housed at the Institute for Clinical and Evaluative Sciences (ICES) to perform a retrospective population-based cohort study with the intent of deciphering the extent of the chemopreventative effect of various putative chemopreventative medications in PCa, specifically in men aged 66 or above in Ontario, with a history of a single negative PB and no prior use of any of the analyzed medications. The results of these analyses will be published elsewhere. For this study, our goal was to assess the associations of the various subgroups of statins, adjusting for other commonly prescribed medications, with UR and LUTS rates within 30 days of a PB, and undergoing a TURP procedure.

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 the accurate capture of all provided prescriptions in the analyzed population.

**Data sources**

Data were acquired from the datasets housed at ICES[23](#_ENREF_23) and detailed in supplemental Table 1. The retrieved data contained demographic, baseline comorbidity, medication prescription, surgical details, and emergency room details. The data of each patient in each of the various datasets are linkable using a unique encoded identifier.

**Study design and participants**

Only men with a minimum age of 66 years and with a history of one single negative transrectal ultrasound-guided PB in the province of Ontario between January 1st, 1994, and September 30th, 2016, were included. The age cut-off of 66 was used to enable a one-year look-back period, confirming that no drug prescription of any of the analyzed medications was given during a minimum period of one year. This ensured that all men analyzed in the study were medication-naïve before study inclusion. For the purpose of identification of all relevant patients, OHIP billing codes for TRUS-Bx, 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 biopsy. The codes used 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, seen fit to undergo a PB, and since they were at an increased risk to develop PCa, which was the main outcome of interest in our primary analysis. 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 ascertain that included men had only a single negative PB and did not have PCa. The index date was defined as 90 days after the date of the single negative PB to ensure no PCa diagnosis.

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 outcome was urinary catheter insertion due to UR within 30 days of a PB, examined as a time to event outcome. Secondary outcomes included experiencing LUTS, manifested as urinary difficulty within 30 days of a PB that required a referral to an emergency department, and rates of TURP at any stage following a PB. For the TURP analysis, only patients who were not diagnosed with PCa were included to exclude PCa patients who underwent “channel TURP”.

**Study variables**

Data on several commonly prescribed medications were acquired. 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 were 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, as the exact age was not provided for discretion reasons), rurality index (continuous variable, with a higher number representing a more rural area)[24](#_ENREF_24), 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)[25](#_ENREF_25), and medically treated diabetes (binary variable indicating whether a man had medically treated diabetes with either metformin, sulfonylurea, thiazolidinedione, or insulin). A three-year look-back period at study inclusion date was used to capture the comorbidity score of each man.

**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 three distinct 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[26](#_ENREF_26). To obtain information on general medication exposure, and on cumulative 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 to 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 group, diabetes indicator, and the following continuous variables with log-linear effects: rurality index (0-100), index year (1994-2016), and the 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, and after using Bonferroni correction due to multiple comparisons (14), a p-value of < (0.05/14 = 0.0035) was considered significant. All statistical analyses were performed using R software version 3.3.1.

**Results**

Between 1994 and 2016, a total of 21,512 men 66 years or older in Ontario with a history of a single negative PB and no previous treatment with any of the analyzed medications were identified. 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 1 depicts the use of commonly prescribed medications among study participants, stratified by duration of use. The most commonly used medications included PPIs (51.3%) alpha-blockers (39.5%), and hydrophobic statins (30.7%), with 19.6% using hydrophilic statins. Figure 1 shows the number of additional biopsies that men underwent during the study period. A total of 35.1% and 11.8% of men underwent at least one and two additional PBs, respectively. A total of 5,187 patients (24.1%) were diagnosed with PCa, while 805 patients (3.7%) died from it, as detailed in Supplemental Figure 2. Figure 2 depicts the percentages of the primary and secondary outcomes, showing a UR and LUTS rate within 30 days of a PB of 2.2%, and 10%, respectively. Additionally, the TURP rate following a PB was 18.5%.

Table 2 shows the multivariable Cox models assessing the primary outcome of UR within 30 days following a PB. These models demonstrated that medically treated diabetes (HR 1.980, 95% CI 1.443-2.716), increased number of previous biopsies (HR 1.170, 95% CI 1.055-1.297) and any use of alpha-blockers (HR 1.800, 95% CI 1.434-2.263) were associated with an increased hazard of having UR. In contrast, a more contemporaneous study inclusion year (HR 0.966, 95% CI 0.945-0.989), and any use of hydrophilic statins (HR 0.561, 95% CI0.380-0.830) were associated with a decreased hazard of UR. Hydrophobic statins did not demonstrate any such association (HR 1.23, 95% CI 0.972-1.579).

Table 3 shows the multivariable Cox models assessing the outcome of having LUTS within 30 days following a PB. Increasing age (80-84 years) compared to age 66-69 years (HR 1.458, 95% CI 1.184-1.796), a more contemporaneous index year (HR 1.066, 95% CI 1.055-1.077), any treatment with alpha-blockers (HR 1.979, 95% CI 1.800-2.176) and every six months use of alpha-blockers (HR 1.048, 95% CI 1.038-1.058) were associated with an increased hazard of having LUTS. However, any use of 5ARIS (HR 0.800, 95% CI 0.705-0.907) and every six months' cumulative use of 5ARIs (HR 0.939, 95% CI 0.920-0.959) were associated with a decreased hazard of having LUTS. Any use and every six months cumulative use of hydrophilic statins were associated with a decreased hazard of having LUTS, although not reaching the required Bonferroni statistical significance level (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. Hydrophobic statins did not demonstrate this association.

Table 4 demonstrates the Cox multivariable models assessing the final secondary outcome of undergoing TURP. An increasing number of cumulative prostate biopsies (HR 1.190, 95% CI 1.130-1.252), any use of 5ARIs (HR 1.523, 95% CI 1.345-1.721), any use of alpha-blockers (HR 2.632, 95% CI 2.403-2.884), and every six months cumulative use of alpha-blockers (HR 1.070, 95% CI 1.058-1.081) were associated with an increased hazard of undergoing TURP. In contrast, a more contemporaneous study inclusion year (HR 0.916, 95% CI 0.908-0.925) was associated with a decreased hazard of undergoing TURP. None of the statin subgroups were shown to have a statistically significant association with undergoing TURP. Lastly, no association between the tracer medication (glaucoma eye drops) and any of the study outcomes were evident.

**Discussion**

Our study showed that 35.1% of Ontarian men aged 66 or above with a single negative PB and no prior use of the examined medications had at least one additional PB during a 20-year follow-up period. The UR and LUTS rate within 30 days of a PB was 2.2%, and 10%, respectively. Additionally, the TURP rate was 18.5% after a median follow-up of 9.4 years (IQR 8). An increasing number of previous biopsies was associated with a higher likelihood of UR and TURP. In contrast to hydrophobic statins, hydrophilic statins were associated with a decreased likelihood of UR and LUTS within 30 days of a PB. 5ARIs were associated with a decreased likelihood of LUTS and increased risk of undergoing TURP. Alpha-blockers were associated with an increased rate of UR, LUTS, and undergoing TURP.

The rate of UR following one single PB is reported to be 1%[16](#_ENREF_16). However, we report on a population of men that 35% of them had at least two PBs, with 11.8% undergoing three PBs, potentially explaining the higher rate of retention shown in our study (2.2%). It has also been shown that 12% and 8% of men undergoing PB reported subjective mild and moderate LUTS on postoperative day 7, respectively[27](#_ENREF_27). This is very similar to our reported result of a 10% prevalence. According to the Agency for Healthcare Research and Quality (AHRQ), in 2014, there were 85,100 TURP procedures performed in the US, representing 26.8 cases performed per 100,000 population[28](#_ENREF_28). This is lower than the reported 18.5% of TURP cases performed in our analyzed population. However, this is not unexpected, as these were men with at least one negative PB, who were followed by urologists, with more than a third of them undergoing at least two PB. Moreover, almost 40% and 23% of them were treated with alpha-blockers and 5ARIs, respectively. In other words, a large proportion of these men had significant LUTS, increasing their risk of undergoing a TURP.

There are contradicting data on the association of statins with LUTS and BPH. A Japanese study showed a significant association between statins and new-onset storage LUTS[29](#_ENREF_29). In a randomized double-blinded, placebo-controlled trial, atorvastatin, a hydrophobic statin, was not shown to be effective in improving LUTS over a 6-month period[30](#_ENREF_30). Additionally, the combination of lovastatin, another hydrophobic statin, with finasteride, a 5ARI, was not shown to improve LUTS after four months of treatment[31](#_ENREF_31). Contrasting these findings, there are several studies showing a significant protective association betwee statins and LUTS. A randomized prospective study randomizing 135 BPH patients with metabolic syndrome to receive statins or placebo for 12 months showed that statin-treated patients had significantly reduced IPSS scores and prostate volumes, compared to placebo-treated patients[32](#_ENREF_32). In a large retrospective analysis, statin use was associated with 6.5-7 years delay in new-onset of LUTS and BPH[33](#_ENREF_33). A study from the Boston Area Community Health (BACH) Survey[19](#_ENREF_19) found that although no protective association was observed between statins and LUTS among women and younger men (<60 years), older men (>60 years), demonstrated a significant inverse association with LUTS[19](#_ENREF_19), 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 the risk of BPH in patients older than 60 years[34](#_ENREF_34).

The etiology behind the suggested beneficial association of statins and LUTS is unknown. Possible mechanisms include 1) reduction of ischemia, 2) anti-inflammatory and 3) anti-angiogenesis effect and 4) decrease of prostate specific antigen (PSA) levels. Bladder outlet obstruction (BOO) resulting from BPH can trigger ischemia during detrusor contraction[35](#_ENREF_35). This eventually leads to impaired contractility, and escalating voiding and storage symptoms[36](#_ENREF_36). It has been suggested that by reducing vasculature atherosclerosis in bladder blood vessels, statins reduce the impact of BOO, lowering the resulting ischemia and preventing LUTS development[19](#_ENREF_19). Il-6 has been shown to be elevated in patients with metabolic syndrome and has also been shown to be increased in men with BPH resulting in prostatic tissue proliferation[37](#_ENREF_37), suggesting that the metabolic syndrome might be contributing to the inflammation seen in men with BPH and LUTS. Statins have been shown to have an anti-inflammatory effect by decreasing IL-6 levels[38](#_ENREF_38) and significantly reducing the proliferation rate of prostate cells[39](#_ENREF_39). Moreover, using data from the REDUCE trial, Allott et al. reported that statin use was associated with decreased histological prostate inflammation, specifically among men with a negative PB, similar to our own study population[40](#_ENREF_40). Statins have also been shown to harbor anti-angiogenesis effects and inhibit capillary formation, reducing the release of vascular endothelial growth factor and improving LUTS[41](#_ENREF_41). Lastly, statins were noted to be associated with reduced PSA levels[42](#_ENREF_42), and as these are correlated with prostate volumes, it has been suggested that statin use might be associated with lower prostate volumes, leading to decreased LUTS[33](#_ENREF_33).

The varying lipophilicity of hydrophobic and hydrophilic statins cause their different pleiotropic effects[43](#_ENREF_43). This changes their solubility and localization, ultimately resulting in considerable metabolic changes[44](#_ENREF_44). Hydrophilic statins are hepato-specific, using carrier-mediated mechanisms for hepatic cell uptake[45](#_ENREF_45). Some of these carriers are extra-hepatic and can be found in the prostate, enabling uptake[46](#_ENREF_46). In contrast, hydrophobic statins passively diffuse into various cells and are widely distributed. A possible explanation for the contradicting findings regarding the association of statins to LUTS could be the fact that statins were either analyzed as one single group[29](#_ENREF_29) or that only hydrophobic statins were analyzed[30](#_ENREF_30),[31](#_ENREF_31), which have not been shown to have a protective association in our study as well. Perhaps the potential mechanisms previously discussed, resulting in a favorable association with LUTS, are uniquely relevant to hydrophilic and not hydrophobic statins.

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

The strengths of our study lie in its large cohort of men treated in the same health system over a relatively long period of time, all initiating treatment with the analyzed medications at study inclusion and not before that. Additionally, to our knowledge, this is the only study specifically assessing the association of each subgroup of statins with LUTS, adjusting for other commonly prescribed medications. Nonetheless, some important limitations need to be mentioned. 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. Second, are the potential inaccuracies embedded in health administrative databases like the ones used in this study. Third, our data was limited to men older than 66, as we could not provide data on younger men. Fourth, clinically important information, including race, PSA levels, prostate volume, prebiopsy IPSS score, and bladder function, were not available. Fifth, diabetes was defined as medically treated diabetes only, and for this analysis, non-medically treated diabetic patients were not included. Lastly, the risk of unaccounted residual confounding is always present.

**Conclusions**

The initiation of hydrophilic statin in men older than 66 at risk for PCa, appears to be inversely associated with the hazard of UR and LUTS within 30 days of a PB. The mechanism by which hydrophilic and not hydrophobic statin harbor this association needs further research. Upon validation of these findings in other large cohorts, men treated with statins may gain more than a cholesterol-lowering effect if they are preferentially treated with hydrophilic statins.

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**Abbreviations:**

5ARIs = Five alpha-reductase inhibitors

ADG = Ambulatory Diagnostic Groups

BOO = Bladder Outlet Obstruction

BPH = Benign prostatic hyperplasia

ICES = Institute for Clinical and Evaluative Sciences

IPSS = International Prostate Symptom Score

IQR = Interquartile range

LUTS = Lower urinary tract symptoms

ODB = Ontario drug benefit

OHIP = Ontario health insurance plan

PB = Prostate biopsy

PCa = Prostate cancer

PPIs = Proton pump inhibitors

PSA = Prostate specific antigen

TURP = Transurethral resection of prostate

UR = Urinary retention

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Writing of manuscript: HG

Editing and reviewing of manuscript: FKM, SA, CJDW, ZK, TC, AEA, OS, GSK, NF

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**Figure legends:**

Figure 1 - Additional prostate biopsies stratified by age:

Figure 2 – Percentage of urinary retention and lower urinary tract symptoms within 30 days of the prostate biopsy and TURP among men stratified by age: