Title

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Journal

Canadian Urological Association journal = Journal de l'Association des urologues du Canada, 16(5)

ISSN

1911-6470

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Publication Date

2022-05-01

DOI

10.5489/cuaj.7464

Peer reviewed

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

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Cite as: Goldberg H, Mohsin FK, Chandrasekar T, et al. The association of statin subgroups with lower urinary tract symptoms following a prostate biopsy. *Can Urol Assoc J* 2022;16(5):E248-55. http://dx.doi.org/10.5489/cuaj.7464

Published online December 21, 2021

Appendix available at *cuaj.ca*

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 (PBx), 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 PBx 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 PBx. 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 PBx. 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 PBx.

Introduction

Transrectal ultrasound (TRUS)-guided prostate biopsy (PBx) is still considered the gold standard approach for prostate cancer (PCa) diagnosis.[1] PBx is one of the most commonly performed urological procedures, with over one million procedures performed yearly in the U.S.[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 (UTI) (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 PBx 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 5–7 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 types: hydrophilic (pravastatin and rosuvastatin) and hydrophobic (simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin).[13] Both subgroups have similar cholesterol reduction effect but exhibit different pleiotropic effects, reflecting their distinct lipophilicity. This, in turn, affects their pharmacokin-

etic 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 [OR] 0.15, 95% confidence interval [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 PCa chemoprevention in men who have had a single negative PBx. 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 PBx, 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 years or above in Ontario, Canada, with a history of a single negative PBx and no prior use of any of several various putative PCa chemopreventative medications as part of our original analysis.[19] As previously mentioned, we used 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 PBx.

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 Supplementary Table 1 (available at *cuaj.ca*) The retrieved data contained demographic, baseline comorbidity, medication prescription, and data on UR and LUTS within 30 days of a PBx. 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 TRUS-guided PBx between January 1, 1994, and September 30, 2016. The age cutoff 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-naive at inclusion. To identify all relevant patients, OHIP billing codes for TRUS-guided PBx 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 PBx. The codes used for this study are detailed in Supplementary Table 2 (available at *cuaj.ca*). Men with a history of a previous negative PBx were chosen as part of a screening method to include a 'healthier' population since they were seen fit enough to undergo a PBx. 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 PBx 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 PBx. 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 30, 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 PBx, 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 (5-ARIs), alpha-blockers, and proton pump inhibitors (PPIs). 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 followup, 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

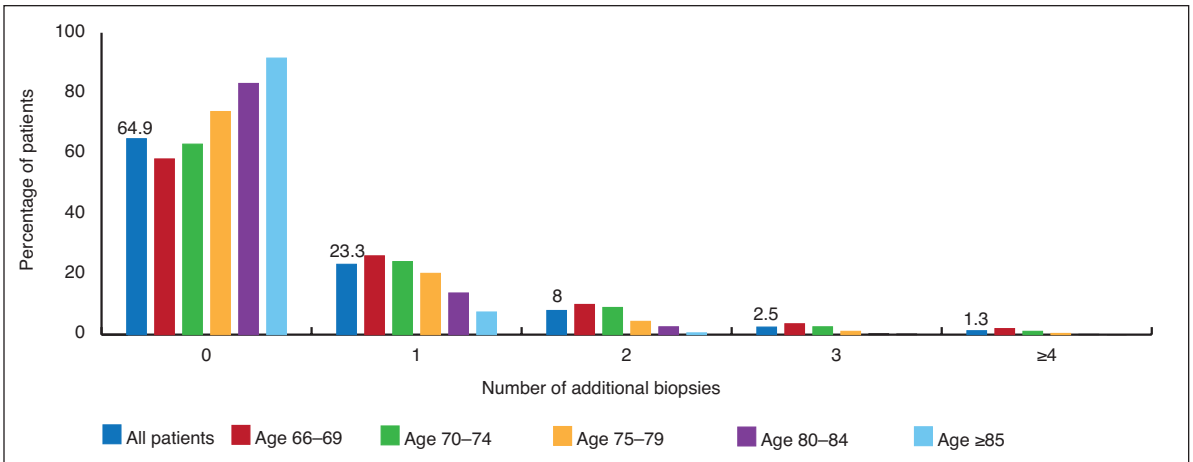
Between 1994 and 2016, 21 512 Ontarian men 66 years or older with a history of a single negative PBx and no previous treatment with any of the analyzed putative chemopreventative medications were identified. The study's consort diagram is shown in Supplementary Figure 1 (available at *cuaj.ca*). The median followup time was 9.4 years (interquartile range [IQR] 8). Table 1 depicts basic demographic data of all men at study inclusion stratified by age category. Supplementary Figure 2 (available at *cuaj.ca*) depicts the use of commonly prescribed medications among study participants stratified by duration of use. The most used medications included 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 PBxs, respectively. In the 30 days following an additional PBx, 466 patients (2.2%) experienced UR requiring catheterization, and 2159 patients (10%) experienced LUTS (Figure 2).

Multivariable Cox proportional hazard modeling demonstrate that any use of hydrophilic statins (hazard ratio [HR] 0.561, 95% CI 0.380–0.830, p=0.0038) was associated with

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, n (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.



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)	11111(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

Figure 1. Additional prostate biopsies stratified by age.

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).

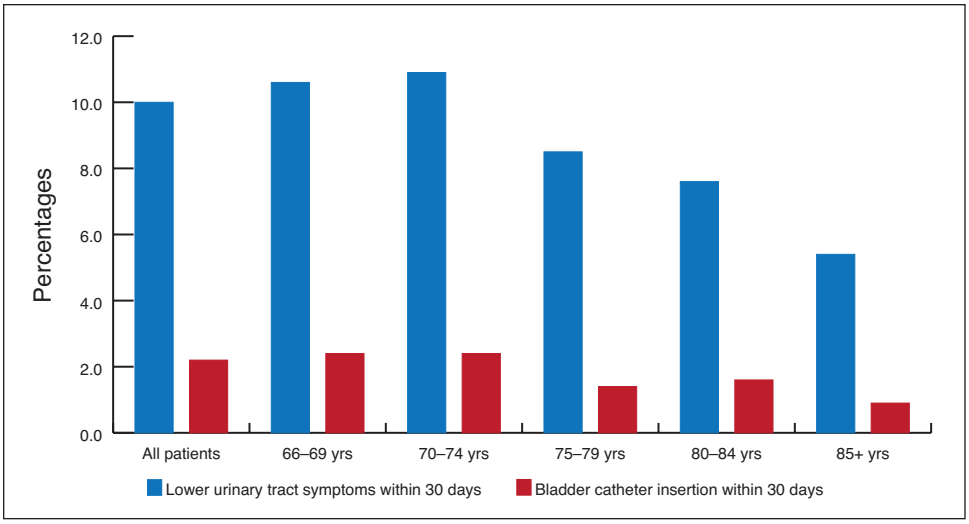


Figure 2. Percentage of urinary retention and lower urinary tract symptoms within 30 days of the prostate biopsy among men stratified by age.

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 (Table 3). 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

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-month usage

	Medications modeled as ever vs. never		Medications modeled using cumulative 6-month 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
5-ARIs	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.

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 5-ARIs (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).

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-month usage

	Medications modeled as ever vs. never		Medications modeled using cumulative 6-month 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
5-ARIs	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.

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 PBx and had no prior use of the analyzed medications had at least one additional PBx during a 20-year followup period. The UR and LUTS rates within 30 days of a PBx 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 PBx, while no such association was seen with hydrophobic statins. As expected, 5-ARIs 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 PBx is reported to be 0.2–1.7%;[4,6] however, in our reported population, 35% of men had at least two PBxs, and 11.8% underwent three PBxs 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 5-ARIs, 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 PBx experience mild and moderate LUTS, respectively, one week following PBx.[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 six-month period.[28] Additionally, when compared to finasteride (a 5-ARI) alone, the combination of lovastatin (another hydrophobic statin) with finasteride was not shown to reduce LUTS more, or further decrease prostate volume or prostate-specific antigen (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 a 6.5–7-year 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 (OR 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, including: 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 PBx, 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.

Study strengths and limitations

Our study's validity is demonstrated by the clear associations shown between use of alpha-blockers and 5-ARIs with LUTS,

the association between the cumulative number of PBxs 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-naive 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 PBx, prone to undergo more PBxs, 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, PBx 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 PBx. 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 on LUTS and UR, especially if they undergo a PBx.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

Acknowledgements: This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding source. No endorsement by ICES of the Ontario MOHLTC is intended or should be inferred. The datasets used in this study were linked using unique encoded identifiers and analyzed at ICES. Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors, and not necessarily those of CIHI. Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred. The authors would like to thank IMS Brogan Inc. for use of their Drug Information Database.

This paper has been peer-reviewed.

References

1. Liss MA, Ehdaie B, Loeb S, et al. An update of the American Urological Association white paper on the prevention and treatment of the more common complications related to prostate biopsy. *J Urol* 2017;198:329-34. https://doi.org/10.1016/j.juro.2017.01.103
2. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. *Eur Urol* 2013;64:876-92. https://doi.org/10.1016/j.eururo.2013.05.049
3. Harvey CJ, Pilcher J, Richenberg J, et al. Applications of transrectal ultrasound in prostate cancer. *Br J Radiol* 2012;85:S3-17. https://doi.org/10.1259/bjr/56357549
4. Lee SH, Chen SM, Ho CR, et al. Risk factors associated with transrectal ultrasound-guided prostate needle biopsy in patients with prostate cancer. *Chang Gung Med J* 2009;32:623-7. http://cgmj.cgu.edu.tw/3206/320605.pdf
5. Wagenlehner FM, van Oostrum E, Tenke P, et al. Infective complications after prostate biopsy: Outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective, multinational, multicenter prostate biopsy study. *Eur Urol* 2013;63:521-7. https://doi.org/10.1016/j.eururo.2012.06.003
6. Pinkhasov GI, Lin YK, Palmerola R, et al. Complications following prostate needle biopsy requiring hospital admission or emergency department visits – experience from 1000 consecutive cases. *BJU Int* 2012;110:369-74. https://doi.org/10.1111/j.1464-410X.2011.10926.x
7. Glaser AP, Novakovic K, Helfand BT. The impact of prostate biopsy on urinary symptoms, erectile function, and anxiety. *Curr Urol Rep* 2012;13:447-54. https://doi.org/10.1007/s11934-012-0277-6
8. Helfand BT, Glaser AP, Rimar K, et al. Prostate cancer diagnosis is associated with an increased risk of erectile dysfunction after prostate biopsy. *BJU Int* 2013;111:38-43. https://doi.org/10.1111/j.1464-410X.2012.11268.x
9. Peyromaure M, Ravery V, Messas A, et al. Pain and morbidity of an extensive prostate 10-biopsy protocol: A prospective study in 289 patients. *J Urol* 2002;167:218-21. https://doi.org/10.1016/S0022-5347(05)65416-X
10. Nam RK, Saskin R, Lee Y, et al. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *J Urol* 2010;183:963-8. https://doi.org/10.1016/j.juro.2009.11.043
11. Zaytoun OM, Anil T, Moussa AS, et al. Morbidity of prostate biopsy after simplified vs. complex preparation protocols: Assessment of risk factors. *Urology* 2011;77:910-4. https://doi.org/10.1016/j.urology.2010.12.033
12. Eisenberg DA. Cholesterol lowering in the management of coronary artery disease: The clinical implications of recent trials. *Am J Med* 1998;104:2s-5s. https://doi.org/10.1016/S0002-9343(98)00038-2
13. Fong CW. Statins in therapy: Understanding their hydrophilicity, lipophilicity, binding to 3-hydroxy-3-methylglutaryl-CoA reductase, ability to cross the blood brain barrier and metabolic stability based on electrostatic molecular orbital studies. *Eur J Med Chem* 2014;85:661-74. https://doi.org/10.1016/j.ejmech.2014.08.037
14. St Sauver JL, Jacobsen SJ, Jacobson DJ, et al. Statin use and decreased risk of benign prostatic enlargement and lower urinary tract symptoms. *BJU Int* 2011;107:443-50. https://doi.org/10.1111/j.1464-410X.2010.09598.x
15. Hall SA, Chiu GR, Link CL, et al. Are statin medications associated with lower urinary tract symptoms in men and women? Results from the Boston Area Community Health (BACH) survey. *Ann Epidemiol* 2011;21:149-55. https://doi.org/10.1016/j.annepidem.2010.09.002

16. Bratslavsky G, Whitbeck C, Horan P, et al. Effects of in-vivo ischemia on contractile responses of rabbit bladder to field stimulation, carbachol, ATP and KCl. *Pharmacology* 1999;59:221-6. https://doi.org/10.1159/000028323
17. Berthold HK, Berneis K, Mantzoros CS, et al. Effects of simvastatin and ezetimibe on interleukin-6 and high-sensitivity C-reactive protein. *Scand Cardiovasc J* 2013;47:20-7. https://doi.org/10.3109/14017431.2012.734635
18. Hindler K, Cleeland CS, Rivera E, et al. The role of statins in cancer therapy. *Oncologist* 2006;11:306-15. https://doi.org/10.1634/theoncologist.11-3-306
19. Goldberg H, Mohsin FK, Saskin R, et al. The suggested unique association between the various statin subgroups and prostate cancer. *Eur Urology Focus* 2021;7:537-45. https://doi.org/10.1016/j.euf.2020.06.005
20. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573-7. https://doi.org/10.7326/0003-4819-147-8-200710160-00010
21. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12:e1001885. https://doi.org/10.1371/journal.pmed.1001885
22. Institute of Clinical Evaluative Sciences Homepage. 2019. Available at: http://www.ices.on.ca. Accessed December 21, 2021.
23. B. K. Measuring Rurality - RIO2008_BASIC: Methodology and Results. 2009. Available at: https://docplayer.net/91599736-Measuring-rurality-rio2008_basic-methodology-and-results.html. Accessed December 21, 2021.
24. H J. The Johns Hopkins ACG System- Excerpt from Technical Reference Guide Version 9.0 2014. Available at: https://www.healthpartners.com/ucm/groups/public/@hp/@public/documents/documents/dev_057914.pdf. Accessed December 21, 2021.
25. Noordzij M, Leffondre K, van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transplant* 2013;28:2670-7. https://doi.org/10.1093/ndt/gft355
26. Emberton M, Anson K. Acute urinary retention in men: an age old problem. *BMJ* 1999;318:921-5. https://doi.org/10.1136/bmj.318.7188.921
27. Zisman A, Leibovici D, Kleinmann J, et al. The impact of prostate biopsy on patient well-being: A prospective study of voiding impairment. *J Urol* 2001;166:2242-6. https://doi.org/10.1016/S0022-5347(05)65543-7
28. Mills IW, Crossland A, Patel A, et al. Atorvastatin treatment for men with lower urinary tract symptoms and benign prostatic enlargement. *Eur Urology* 2007;52:503-9. https://doi.org/10.1016/j.eururo.2007.02.032
29. Stamatiou KN, Zaglavira P, Skolarikos A, et al. The effects of lovastatin on conventional medical treatment of lower urinary tract symptoms with finasteride. *Int Braz J Urol* 2008;34:555-61;discussion 61-2. https://doi.org/10.1590/S1677-55382008000500003
30. Zhang X, Zeng X, Dong L, et al. The effects of statins on benign prostatic hyperplasia in elderly patients with metabolic syndrome. *World J Urol* 2015;33:2071-7. https://doi.org/10.1007/s00345-015-1550-3
31. Yang X, Zhang Q, Jiang G, et al. The effects of statins on benign prostatic hyperplasia and the lower urinary tract symptoms: A meta-analysis. *Medicine* 2019;98:e15502. https://doi.org/10.1097/MD.0000000000015502
32. Azadzoi KM, Tarcan T, Kozlowski R, et al. Overactivity and structural changes in the chronically ischemic bladder. *J Urol* 1999;162:1768-78. https://doi.org/10.1016/S0022-5347(05)68236-5
33. Fibbi B, Penna G, Morelli A, et al. Chronic inflammation in the pathogenesis of benign prostatic hyperplasia. *Int J Androl* 2010;33:475-88. https://doi.org/10.1111/j.1365-2605.2009.00972.x
34. Sun Y, Sukumaran P, Varma A, et al. Cholesterol-induced activation of TRPM7 regulates cell proliferation, migration, and viability of human prostate cells. *Biochimica et Biophysica Acta* 2014;1843:1839-50. https://doi.org/10.1016/j.bbamcr.2014.04.019
35. Allott EH, Howard LE, Vidal AC, et al. Statin use, serum lipids, and prostate inflammation in men with a negative prostate biopsy: Results from the REDUCE trial. *Cancer Prev Res (Phila)* 2017;10:319-26. https://doi.org/10.1158/1940-6207.CAPR-17-0019
36. Cyrus-David MS, Weinberg A, Thompson T, et al. The effect of statins on serum prostate specific antigen levels in a cohort of airline pilots: A preliminary report. *J Urol* 2005;173:1923-5. https://doi.org/10.1097/01.ju.0000158044.94188.88
37. Bonsu KO, Kadirvelu A, Reidpath DD. Lipophilic vs. hydrophilic statin therapy for heart failure: A protocol for an adjusted indirect comparison meta-analysis. *Syst Rev* 2013;2:22. https://doi.org/10.1186/2046-4053-2-22
38. Mason RP, Walter MF, Day CA, et al. Intermolecular differences of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors contribute to distinct pharmacologic and pleiotropic actions. *Am J Cardiol* 2005;96:11f-23f. https://doi.org/10.1016/j.amjcard.2005.06.008
39. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: An update. *Fund Clin Pharmacol* 2005;19:117-25. https://doi.org/10.1111/j.1472-8206.2004.00299.x
40. Schuster VL. Prostaglandin transport. *Prostaglandins Other Lipid Mediat* 2002;68-69: 633-47. https://doi.org/10.1016/S0090-6980(02)00061-8

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