**SHOULD WE PRESCRIBE ONLY A SPECIFIC STATIN TO MEN?**

**THE SUGGESTED UNIQUE ASSOCIATION BETWEEN THE VARIOUS STATIN SUBGROUPS AND PROSTATE CANCER**

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**Abstract**

**Background**

The chemopreventative effect of various medications in prostate cancer (PCa) has gained interest. Specifically, the potential impact of statins on PCa incidence has been studied, but solely as a ‘drug family’ overlooking the distinctive pharmacological properties of its two main subgroups: hydrophilic and hydrophobic statins.

**Objective**

To assess the impact of statin subgroups on PCa specific mortality (PCSM), PCa diagnosis, and undergoing another prostate biopsy.

**Design, Setting and Participants**

A population-based cohort study in Ontario identifying all men aged 66 and above with a history of a single negative prostate biopsy (representing healthy men at risk for PCa) between 1994 and 2016, who were not on any of the analyzed medications prior to the study, with a median follow-up of 9.42 years (IQR 8.03 years).

**Outcome Measurement and Statistical Analysis**

Using multivariable Cox-regression models with time-dependent covariates, the association of hydrophobic and hydrophilic statins with all study outcomes were analyzed. Other putative chemopreventative medications including alpha-blockers, five-alpha-reductase inhibitors, and proton-pump inhibitors, age, rurality, comorbidities, and study inclusion year were included in the models.

**Results and limitations**

Overall 21,512 men were identified. Statins were taken by 11,401 patients (50.3%), 5,184 men (24.1%) were diagnosed with PCa, and 805 (3.7%) died from it. Overall, 7,556 patients (35.1%) underwent another biopsy. Any use of hydrophilic statins was associated with a 32.4% (95% CI 12.9-47.5%), 20% (95% CI 10-28%), and 18% (95% CI 6.1-27.3%), decreased risk of PCSM, undergoing another prostate biopsy, and being diagnosed with PCa, respectively. Hydrophobic statins were associated with a 17% (95% CI 2-31%) decreased PCSM. The study is limited by its retrospective nature, selection bias, and accompanying health-administrative database inaccuracies.

**Conclusions**

Use of any statin may be associated with a lower hazard of PCSM, with hydrophilic statins showing a greater association with decreased PCa diagnosis rates. Preferentially prescribing one statin subgroup over another in men needs further exploration.

**Patient summary**

Use of any statin may be associated with a lower probability of dying from prostate cancer. Hydrophilic statins (rosuvastatin and pravastatin) may also be more positively associated with a lower risk of undergoing an additional prostate biopsy and being diagnosed with prostate cancer in men aged 66 or above.

**Introduction**

Prostate cancer (PCa) is the most common non-cutaneous cancer diagnosed in North-American men[1](#_ENREF_1). The American Cancer Society estimates that in 2019, approximately 174,650 new cases will be diagnosed, and 31,620 cancer-specific deaths will occur in the US[1](#_ENREF_1). Approximately 60% of PCa develop in men older than 65, with an average age of 66[1](#_ENREF_1).

Multiple medications have been assessed regarding their role in primary and secondary PCa prevention. These include 5-alpha-reductase-inhibitors[2](#_ENREF_2), alpha blockers[3](#_ENREF_3), proton pump inhibitors (PPIs)[4](#_ENREF_4) and statins[5](#_ENREF_5). The role of statins in PCa and other malignancies has been extensively studied, albeit mostly as a ‘drug family’ without consideration of existing subgroups with distinct pharmacological properties.

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoAR) inhibitors, are mainly used to improve lipid profiles and reduce cardiovascular morbidity and mortality[6](#_ENREF_6). However, statins may also have a cancer chemopreventative role as reduction in cholesterol availability may limit the cellular proliferation required for cancer growth and metastasis[5](#_ENREF_5). HMGCoAR is the rate-limiting enzyme of the mevalonate pathway, which is integral for cell growth and survival[7](#_ENREF_7). Statins can be divided into hydrophilic (pravastatin and rosuvastatin) and hydrophobic (simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin) statins[8](#_ENREF_8). Although both groups have similar cholesterol reduction effect, they hold different pleiotropic effects, caused by the variance in their lipophilicity.

Recent in-vitro experiments demonstrated that HMGCoAR inhibition, caused by hydrophilic statins, was insufficient to induce apoptosis in most PCa cell lines[9](#_ENREF_9). However, sensitivity to fluvastatin, a hydrophobic statin, was inversely associated with mevalonate pathway activation following statin treatment, leading to increased PCa cell death[9](#_ENREF_9). Additionally, dipyridamole, an anti-platelet medication, potentiated fluvastatin-induced apoptosis in PCa cells[9](#_ENREF_9).

This led us to investigate the association of hydrophilic and hydrophobic statins in the context of other putative PCa influential medications in men who were at an increased risk of developing PCa. We hypothesized that both statin subgroups would have a protective association, and based on the above mentioned in-vitro evidence[9](#_ENREF_9), hydrophobic stains might have a more significant association than hydrophilic statins with decreased PCa-specific mortality (PCSM) and PCa diagnosis.

**Methods**

This study was approved by the University of Toronto’s ethics board committee. The study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines[10](#_ENREF_10), and Reporting of Studies Conducted Using Observational Routinely-Collected Health Data Statement[11](#_ENREF_11). We performed a retrospective population-based cohort study using administrative data housed at the Institute for Clinical and Evaluative Sciences (ICES). In Ontario, all essential medical care is reimbursed by a single, government-operated health insurance system, the Ontario Health Insurance Plan (OHIP), enabling us to capture the entire adult population. Moreover, everyone 65 years and older is eligible for prescription drug coverage through the Ontario Drug Benefit (ODB) program, enabling accurate capture of all prescriptions provided.

**Data sources**

Data were acquired from several specific datasets housed at ICES and detailed in supplemental Table 1. The retrieved data contained demographic, baseline comorbidity, medication prescription, cancer diagnosis, and vital status details. Patient-specific information from these databases is linkable using unique, encoded identifiers.

**Study design, setting, and participants**

We used the age of 66 as the minimum age for study inclusion to enable a one-year look-back period, confirming that no drug prescription of the analyzed medications was provided between the age of 65 and 66 (i.e. all patients included in the analysis had not taken any of the analyzed medications before the study period). We identified all men aged 66 and older with a history of a single negative transrectal ultrasound-guided prostate biopsy (TRUS-Bx) in Ontario, Canada (estimated population of ~14 million) between January 1st, 1994 and September 30th, 2016. Relevant patients were identified using OHIP billing codes for TRUS-Bx, with no evidence of PCa diagnosis, nor receipt of PCa-specific treatment within the following three months after the biopsy, using the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) (Supplemental Table 2). The reason men with a history of a previous negative biopsy were chosen was twofold: 1) These men are at an increased risk to develop PCa as seen in the PLCO trial, showing men with a negative biopsy having a PCa-specific mortality rate of 2.93 fold higher than men in the general population[12](#_ENREF_12) 2) This was used as a pre-screening tool to include a ‘healthier’ population, seen fit to undergo a biopsy. We utilized a look-back window from January 1991 until cohort entry (minimum 3 years, as data were not available before that) to ascertain that included men had only a single negative TRUS-Bx with no previous PCa diagnosis. The index date was defined as the date 90 days after the date of the first negative prostate biopsy (PB) to ensure no PCa diagnosis.

We analyzed the association of hydrophobic and hydrophilic statins on PCa-related outcomes. We analyzed additional medications that may also affect PCa outcomes. These included PPIs, five-alpha-reductase inhibitors, alpha-blockers, dipyridamole and chloroquine. Glaucoma eye drops were included as a tracer drug, serving as a negative control, to show no association with any of the outcomes. A complete list of all medications included in the analysis is shown in Appendix 1.

The follow-up time began with the date of negative TRUS-Bx and continued until death, last health services contact in Ontario, becoming OHIP ineligible, or end of the study period (patients were censored if they were still alive at the end of the study period).

**Study outcomes**

Our primary outcome was PCSM rate. Secondary outcomes included rates of undergoing an additional PB and PCa diagnosis. Patients who were diagnosed with PCa were censored from the analysis of undergoing an additional PB.

**Study variables**

PCa was considered the reason for death if noted as the immediate cause of death on the patient’s death certificate. PCa diagnosis was defined as having either a record of PCa or having received PCa-specific treatment (radical prostatectomy, primary radiotherapy to the prostate or androgen deprivation therapy [ADT]). Active surveillance (AS) per se was not captured. Therefore, if no treatment was noted, we assumed the patient was either on AS, watchful waiting or not treated for some reason. Additional collected variables included age (categories: 66-69, 70-74, 75-79, 80-84, 85 years and above), rurality index (continuous variable with a higher number representing a more rural area)[13](#_ENREF_13), study inclusion year, medically-treated diabetes (binary variable), and comorbidity status quantified with the Collapsed Ambulatory Diagnostic Groups (ADG) score (a continuous comorbidity variable derived from the Johns Hopkins Adjusted Clinical Groups System)[14](#_ENREF_14). Comorbidities were captured with a 3-year look-back period, and Prostate-specific antigen (PSA) levels were available only from 2007.

**Statistical analyses**

Continuous variables were described using means and standard deviations (SD); categorical variables were characterized using proportions. To estimate the associations of any exposure and cumulative exposure per unit of time for all medications, two types of analyses were performed. First, multivariable Cox proportional hazard regression models with time-dependent exposure were used for each cause-specific hazard[15](#_ENREF_15). The exposure to each medication was specified as a time-dependent variable (ever vs. never exposure at any time point during the follow-up). Second, we estimated the association of the cumulative time of taking each medication in six-months intervals. All models included the above mentioned putative PCa influential medications. Additionally, models were adjusted for the person’s age group, rurality index (0-100), index year (1994-2016) and the ADG comorbidity score, with the last three being modeled as continuous variables with log-linear effects. These covariates were selected a priori and were treated as time-independent variables using the values at study onset. For PCa-specific mortality, PCa-specific treatments were incorporated as well (radical prostatectomy, primary radiotherapy, and ADT). The proportional and log-linearity assumptions underlying the models were assessed using residual-based diagnostics, and no violations were identified. 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.

**Sensitivity analyses**

We performed several preplanned sensitivity analyses. We analyzed the associations of all statins combined, and to adjust for PSA levels as well, we used the same analyses but specifically included only patients enrolled from 2007, when PSA became available. If more than one PSA test was available, the median PSA for each patient was used with a limited time-frame of one year from the first negative biopsy date. Additionally, to compare only men treated with statins, we performed an analysis comparing hydrophilic and hydrophobic statin users only with the exposure defined as beginning of statin use. This was done for PCSM and PCa diagnosis. We also performed an additional analysis to assess all cause mortality. Lastly, for dataset validation, a negative control analysis was performed. For this, we assessed the associations of all medications on presbyopia diagnosis.

**Results**

**Medication use and prostate cancer outcomes:**

A total of 21,512 men met our inclusion criteria, with a median follow-up time (IQR) of 9.42 years (8.03 years). Figure 1 shows the flowchart of the final cohort, and Table 1 depicts basic demographic data.

Supplemental Figure 1 highlights the rates of medication usage, showing a high rate of statin use, with 10,818 patients (50.3%) starting a statin medication, with hydrophobic statins being the most common (6,607 patients, [61.1% of statin users]).

Supplemental Figure 2 shows the rates of PCa diagnosis, PC-specific death, and all-cause mortality, while Supplemental Figure 3 highlights the various PCa treatment modalities. A total of 5,187 patients (24.1%) were diagnosed with PCa, and 805 patients (3.7%) died from it. Most PCa patients were on either active surveillance/watchful waiting or not actively treated (1,811 patients, [34.9%]). Lastly, 7,556 patients (35.1%) had at least one additional PB (Supplemental Figure 4).

**Statins and prostate cancer-specific death:**

For PCSM, supplemental table 3 shows that statins combined were associated with a decreased PCSM when medications were specified as ever vs. never (HR 0.76, 95% CI 0.64-0.90, p=0.0018). When specifying each statin group separately (Table 2), both hydrophobic and hydrophilic statins were associated with a lower PCSM, when specified as ever vs. never usage (HR 0.83, 95% CI 0.69-0.98, p=0.032) and (HR 0.68, 95% CI 0.52-0.87, p=0.0024), respectively, although only hydrophilic statins reached the defined Bonferroni statistical significance level. When specified as per six months of cumulative use both hydrophobic statins (HR (0.98, 95% CI 0.97-0.99, p=0.046) and hydrophilic statins (HR 0.96, 95% CI 0.92-0.99, p=0.018), were associated with decreased PCSM, although not reaching the defined statistical significance. A model incorporating PSA values was not done for this outcome as the number of PCSM events from 2007 was too low. Supplemental table 4 shows that compared to hydrophobic statins, hydrophilic statin use was associated with a decreased PCSM (HR 0.88, 95% CI 0.64-1.21, p=0.44), although not showing statistical significance. Supplemental table 5 shows the analysis for all cause mortality, demonstrating that both hydrophilic and hydrophobic statins were associated with decreased all-cause mortality, although hydrophilic statins showed a greater benefit ((HR 0.82, 95 CI 0.77-0.87, p<0.0001) compared to hydrophobic statins (HR 0.94, 95% CI 0.89-0.98, p=0.008)).

**Statins and undergoing an additional prostate biopsy:**

In the model assessing predictors of having an additional PB, only hydrophilic statins were associated with a lower rate of undergoing an additional biopsy, when specified as ever vs. never usage (HR 0.80, 95% CI 0.72-0.90, p=0.0002), and as cumulative six months of use (HR 0.97, 95% CI 0.94-0.99, p=0.0002). Hydrophobic statins did not show any similar association (HR 0.96, 95% CI 0.89-1.03, p=0.3, and HR 0.99, 95% CI 0.98-1.01, p=0.342, respectively) (Table 3). In the sensitivity analysis incorporating only patients with PSA data from 2007, hydrophilic statins were also shown to be associated with a decreased rate of undergoing an additional biopsy (HR 0.71, 95% CI 0.53-0.97, p=0.029), while hydrophobic statins did present this association.

**Statins and prostate cancer diagnosis:**

When assessing PCa diagnosis, supplemental table 6 shows that when both statin groups were combined, they were associated with a reduced hazard of being diagnosed with PCa, when medication use was specified per six months of cumulative use (0.99, 95% CI 0.98-0.99, p=0.046), but this did not reach the defined statistical significance level. However, when we specified each statin group separately, hydrophilic statins were associated with a decreased hazard of being diagnosed with PCa (Table 4), when medications use was specified as ever. vs. never (HR 0.820, 95% CI 0.727-0.939, p=0.003) and when specified per six months of cumulative use (HR 0.973, 95% CI 0.951-0.995, p=0.017). Hydrophobic statins did not have any similar association in these analyses. In the sensitivity analysis incorporating PSA data from 2007, only 2,773 patients (12.9% of the cohort) were included in the analysis and no significant statistical association was noted between hydrophilic and hydrophobic statins and PCa diagnosis. No interaction was done between hydrophilic and hydrophobic statins, as none of the patients had taken them both in the same time (as expected). However, we performed a sensitivity analysis and compared hydrophilic to hydrophobic statin users with the exposure beginning at the time statins were initiated. This analysis (supplemental table 7) showed that hydrophilic statin use compared to hydrophobic statin use was associated with a decreased rate of PCa diagnosis (HR 0.89, 95% CI 0.76-1.05, p=0.168), although not reaching statistical significance.

**Additional covariates and medications:**

As for the other covariates in the models, age was associated with a higher hazard of dying from PCa and a decreased rate of undergoing an additional biopsy. Increasing ADG score and medically treated diabetes were associated with a decreased rate of undergoing a biopsy. Increasing rurality was associated with an increased hazard of being diagnosed with PCa. A more recent index year was associated with a decreased hazard of being diagnosed with PCa, PCa-specific mortality and having an additional biopsy. As expected, higher PSA was associated with an increased hazard of being diagnosed with PCa. Lastly, none of the other medications had shown any protective association with any of the outcomes (Supplemental tables 8-10). A focused assessment of each of these medications, especially for those conferring a worse association with PCa outcomes is beyond the scope of this manuscript and will be considered elsewhere.

**Negative Control model:**

Glaucoma eye drops, serving as a tracer drug, did not demonstrate any association with the study outcomes (Supplemental Tables 8-10). Our negative control model, assessing predictors of being diagnosed with presbyopia is shown in supplemental table 11.

**Discussion**

Our study showed that over a median follow-up time of 9.4 years more than a third of men aged 66 and above with a negative PB had at least one additional biopsy. A total of 24.1% of them were eventually diagnosed with PCa with a 3.7% PCSM rate. This coincides with a previous analysis of men older than 40 with a history of a negative PB, showing a PCa diagnosis rate of 23.7%[16](#_ENREF_16) and a similar PCSM rate as in the “normal” male population[17](#_ENREF_17). More than half of the men in our study had started a statin medication. Our study showed that hydrophilic statin use was associated with a 32.4%, 20% and 18% decreased hazard of PCSM, undergoing an additional PB, and being diagnosed with PCa, respectively. Hydrophobic statin use was associated with a 17% decreased hazard of PCSM, while no statistically significant associations were shown with PCa diagnosis and undergoing a PB. Furthermore, every six-months of taking a hydrophilic statin, was associated with a 4% (95% CI, 1-8, p=0.018), 3% (95% CI 0.80-5.60, p=0.0002), and 3% (95% CI 0.90-4.50, p=0.017), decreased hazard of PCSM, undergoing an additional PB, and being diagnosed with PCa, respectively. While six-months cumulative use of hydrophobic statins was associated with a 2% (95% CI 1-3, P=0.046) decreased hazard of PCSM.

Experimental in-vitro studies have shown that statins manifest antitumor associations by inhibiting cell proliferation, inducing apoptosis and impeding angiogenesis and metastasis[7](#_ENREF_7). HMGCoAR, the enzyme inhibited by statins, catalyzes the conversion of HMG-CoA into mevalonate, a precursor of cholesterol and the isoprenoid intermediates. These isoprenoids are critical in the process of prenylation, facilitating anchoring of proteins to cell-membranes[18](#_ENREF_18), including oncoproteins involved in numerous malignancies[19](#_ENREF_19). The statin-induced inhibition of these processes reduces tumor cell proliferation, destabilizes membrane integrity, and impedes cell signalling[20](#_ENREF_20).

Despite these findings, there have been several clinical studies showing contradictory findings regarding the beneficial role of statins as a group in PCa. Large retrospective studies have shown an association between statins and PSA level reduction[21](#_ENREF_21) (lessening the hazard of being referred for a PB), decreased PCa diagnosis rate[22](#_ENREF_22), longer time to progression during ADT in hormone-sensitive PCa[23](#_ENREF_23), and decreased PCSM[24](#_ENREF_24). In contrast, other studies have shown no beneficial association of statins as a group on PCa diagnosis[25](#_ENREF_25) and on biochemical recurrence rate[26](#_ENREF_26). One possible reason for these contradictory findings is that statins were analyzed as a pooled drug family. There are in-vitro studies showing that hydrophobic statins may be more effective at suppressing micrometastatic outgrowth due to increased uptake into cancer cells[27](#_ENREF_27). However, the only prospective randomized controlled trial comparing a hydrophobic statin (atorvastatin) to placebo before radical prostatectomy did not demonstrate a decreased PCa proliferation rate with atorvastatin[28](#_ENREF_28).

The differences in the pleiotropic effects between hydrophilic and hydrophobic statins are most likely caused by the different lipophilicity, based on the presence or absence of polar moieties on their main hydrophobic structure[29](#_ENREF_29). This affects their solubility and localization, resulting in significant metabolic changes[30](#_ENREF_30). While hydrophobic statins passively diffuse into cells and are widely distributed throughout various tissues, hydrophilic statins are hepato-specific, and employ carrier-mediated mechanisms for hepatic cell uptake[31](#_ENREF_31), using the organic anion transporters (OAT)[8](#_ENREF_8). OATs normally transport endogenous substrates such as steroids, hormones, and neurotransmitters, but can also transport numerous drugs, including hydrophilic statins, antivirals, antibiotics, and anticancer drugs[32](#_ENREF_32). Several OATs are not exclusive to the liver and can be found in various organs, including prostate[33](#_ENREF_33). Additionally, many cancer tissues, including PCa, have abnormal expression of liver-specific OATs[34](#_ENREF_34), enabling direct uptake of hydrophilic statins into the prostate[35](#_ENREF_35). The aberrant overexpression of OATs has been shown to facilitate survival of metastatic prostate lesions during ADT by enabling uptake of critical cell nutrients[34](#_ENREF_34). However, this overexpression also boosts the sensitivity of castrate-resistant tumors towards anticancer medications such as docetaxel, due to its increased uptake.

While there are currently no formal recommendation to prefer one statin over the other, the question if a specific statin subgroup has an oncological association greater than that of the other subgroup has been previously explored only in breast[36](#_ENREF_36), cervical[37](#_ENREF_37), ovarian[38](#_ENREF_38), and hepatic[39](#_ENREF_39) malignancies. In breast cancer, hydrophobic statins were not associated with a lower cancer incidence rate[36](#_ENREF_36), while In cervical cancer, they were associated with improved progression-free- and overall survival[37](#_ENREF_37). In hepatic and ovarian cancer, both hydrophilic and hydrophobic statins were shown to be associated with decreased cancer incidence[39](#_ENREF_39) and improved overall survival[38](#_ENREF_38), respectively. In a very recently published population-based study, hydrophilic statins were associated with an improved overall- and PCSM in a cohort of men with metastatic/advanced PCa on ADT[40](#_ENREF_40). This latter study supports our findings, showing the favorable role of hydrophilic over hydrophobic statins in PCa.

Our study is unique due to its large cohort, consisting of elaborate ‘real-world’ clinical data with relatively long follow-up time. To date, this is the only study specifically assessing the association of hydrophilic and hydrophobic statins to PCSM, PCa diagnosis and undergoing an additional PB. However, our study has several limitations. First, this was a retrospective population-based analysis with its associated selection bias and accompanying health-administrative database inaccuracies. The possible selection bias could have potentially inflated the hazard ratio, as our target population is older than 66, with many of these men being treated with some of the analyzed medications, causing the association of the medications to be greater than it really is. Furthermore, including PCa-specific treatments that occurred after statin use could have induced a selection bias if there were unmeasured factors related to both treatment and PCSM. Second, the data are limited to men older than 66, and contain information on patients who were diagnosed more than twenty years ago, when different PB strategies, were utilized. Third, there is a confounding bias as important clinical data were lacking. These include complete PSA data, details of clinical-stage, grade, prostate imaging, pertinent family history, ethnicity, and biopsy detailed pathology. We also lacked data regarding the clinical indications of statins, body mass index and smoking. Fourth, in a retrospective population based longitudinal study, immortal-time bias always needs to be considered. However, the Cox proportional hazard model with time dependant covariates should address and minimize the effect of this bias[41](#_ENREF_41). Fifth, as this is a study utilizing health administrative databases for research purposes, information bias in the form of misclassification error almost always exists, limiting validity. Sixth, healthcare utilization bias needs to be mentioned as well. Men who use healthcare services more frequently are often referred more for diagnostic tests and tend to be prescribed more medications. This is affected by many factors and could have influenced the number and type of medications received and the likelihood of undergoing a PB and being diagnosed with PCa. Seventh, diabetes was defined as medication-treated diabetes only, and for this analysis, diet-only treated diabetic patients were not considered diabetic. Importantly, in such an analysis, there is always the risk of ascertainment bias and unaccounted residual confounding. This can result from the use of age categories, leaving residual confounding by age, which could be associated with statin use and perhaps the type of statin used.

**Conclusions**

Statins as a group appear to be associated with a decreased rate of PCSM. Moreover, hydrophilic statins might have a unique association with decreased PCa diagnosis. Ideally, randomized controlled studies assessing the association of statins to PCa-specific outcomes would help validate our findings. Barring such trials, we suggest confirmation of our findings in other larger registries.

**Abbreviations:**

ADT = Androgen deprivation therapy

ADG = Ambulatory Diagnostic Groups

AS = Active surveillance

CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database

HMGCoAR = 3-hydroxy-3-methylglutaryl coenzyme A reductase

ICES = Institute for Clinical and Evaluative Sciences

OAT = Organic anion transporters

OCR = Ontario cancer registry

ODB = Ontario drug benefit

OHIP = Ontario health insurance plan

OLIS = Ontario laboratory information system

ORG = Ontario office of the Registrar

RPDB = Registered persons database

PB = Prostate biopsy

PCa = Prostate cancer

PPI = Proton pump inhibitors

PSA = Prostate specific antigen

TRUS BX = Transrectal ultrasound guided prostate biopsy

**Author Contributions:**

Design and conception: HG, NF, SA, GSK, RS

Data collection and analyses: HG, FKM, OS, RS, AB, SH, CJDW, LP, GSK, NF

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**Figure Legends:**

**Figure 1 - Patient flowchart**

Table 1 – Basic Demographic characteristics of all patients:

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Hydrophobic statins** | **Hydrophilic statins** | **No statins** |
| **Number of patients (%)** | 6607 (30.7%) | 4211 (19.6%) | 10694 (49.7%) |
| **Age category, n (%)** |  | | |
| **66-69** | 2909 (44%) | 2118 (50.3%) | 3722 (34.8%) |
| **70-74** | 2411 (36.5%) | 1510 (35.9%) | 3615 (33.8%) |
| **75-79** | 1026 (15.5%) | 481 (11.4%) | 2085 (19.5%) |
| **80-84** | 218 (3.3%) | 92 (2.2%) | 909 (8.5%) |
| **>=85** | 43 (0.7%) | 10 (0.2%) | 363 (3.4%) |
| **Index Year, n (%)** |  | | |
| **1994-2000** | 4337 (65.6%) | 2057 (48.8%) | 5907 (55.2%) |
| **2001-2007** | 1957 (29.6%) | 1629 (38.7%) | 3073 (28.7%) |
| **2008-2014** | 313 (4.7%) | 525 (12.5%) | 1714 (16%) |
| **Rurality index, mean (SD)** | 11.08 (17.28) | 11.94 (17.16) | 11.76 (17.50) |
| **Income quintile, n (%)** |  | | |
| **1** | 1025 (15.4%) | 603 (14.3%) | 1732 (16.2%) |
| **2** | 1246 (18.9%) | 851 (20.2%) | 2042 (19.1%) |
| **3** | 1366 (20.7%) | 841 (20.0%) | 2181 (20.4%) |
| **4** | 1319 (20.0%) | 878 (20.9%) | 2160 (20.2%) |
| **5** | 1624 (24.6%) | 1027 (24.4%) | 2524 (23.6%) |
| **Not available** | 27 (0.4%) | 11 (0.2%) | 55 (0.5%) |
| **Mean ADG score (SD)** | 19.02 (11.17) | 17.75 (10.93) | 19.33 (11.97) |
| **Diabetes, n (%)** | 1258 (19.0%) | 795 (18.9%) | 567 (5.3%) |
| **Cumulative biopsy, n (%)** |  | | |
| **0** | 3896 (59%) | 2506 (59.5%) | 7357 (68.8%) |
| **1** | 1728 (26.2%) | 1087 (25.8%) | 2288 (21.4%) |
| **2** | 614 (9.3%) | 396 (9.4%) | 760 (7.1%) |
| **3** | 235 (3.6%) | 155 (3.7%) | 193 (1.8%) |
| **4 or more** | 134 (2.0%) | 67 (1.6%) | 96 (0.9%) |

Table 2 - Cox proportional hazards multivariable regression model predicting the risk of prostate cancer specific death with medications modeled as ever vs. never and cumulative 6 months usage:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Ever vs. Never** | | **Cumulative 6 months** | |
| **Hazard Ratio (95% C.I)** | **P value** | **Hazard Ratio (95% C.I)** | **P value** |
| **Age category (reference 66-69)** |  |  |  |  |
| **Age 70-74** | ***1.68 (1.34-1.98)*** | ***<0.0001*** | ***1.67 (1.38-2.02)*** | ***<0.0001*** |
| **Age 75-79** | ***3.05 (2.46-3.77)*** | ***<0.0001*** | ***3.15 (2.55-3.90)*** | ***<0.0001*** |
| **Age 80-84** | ***5.25 (3.98-6.93)*** | ***<0.0001*** | ***5.51 (4.18-7.20)*** | ***<0.0001*** |
| **Age >=85** | ***9.79 (6.27-15.28)*** | ***<0.0001*** | ***10.14 (6.50-15.80)*** | ***<0.0001*** |
| **ADG comorbidity score (continuous variable)** | 1.00 (0.99-1.01) | 0.1 | 1.006 (1.00-1.01) | 0.07 |
| **Rurality index (continuous variable)** | 1.00 (1.001-1.008) | 0.01 | 1.00 (1.001-1.008) | 0.01 |
| **Index Year (continuous variable)** | ***0.91 (0.89-0.94)*** | ***<0.0001*** | ***0.92 (0.90-0.95)*** | ***<0.0001*** |
| **Diabetes (vs. no diabetes)** | 1.36 (1.07-1.72) | 0.01 | 1.35 (1.07-1.720) | 0.011 |
| **Prostate cancer treatment (reference no treatment)** |  |  |  |  |
| **Primary curative radiotherapy** | 1.29 (0.89-1.87) | 0.17 | 1.26 (0.87-1.83) | 0.21 |
| **Radical Prostatectomy** | 0.94 (0.62-1.41) | 0.76 | 0.93 (0.62-1.41) | 0.75 |
| **Primary androgen deprivation therapy** | 1.01 (0.79-1.30) | 0.91 | 1.02 (0.79-1.32) | 0.84 |
| **Statin treatment (reference - no statin treatment)** |  |  |  |  |
| **Hydrophobic statins** | 0.83 (0.69-0.98) | 0.032 | 0.98 (0.97-0.99) | 0.046 |
| **Hydrophilic statins** | ***0.68 (0.52-0.87)*** | ***0.0024*** | 0.96 (0.92-0.99) | 0.018 |
| All models were also included usage of proton pump inhibitors, alpha blockers, five-alpha-reductase-inhibitors, Chloroquine, Dipyridamole, and glaucoma eye drops  ADG = Johns Hopkins' Aggregated Diagnosis Groups; PSA = Prostate specific antigen | | | | |

Table 3 - Cox proportional hazards multivariable regression model predicting the risk of having an additional prostate biopsy with medications modeled as ever vs. never and cumulative 6 months usage:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Ever vs. Never** | | **Cumulative 6 months** | | **Ever vs. Never (Only patients with PSA [>2007])** | |
| **Hazard Ratio (95% C.I)** | **P value** | **Hazard Ratio (95% C.I)** | **P value** | **Hazard Ratio (95% C.I)** | **P value** |
| **Age category (reference 66-69)** |  |  |  |  |  |  |
| **Age 70-74** | ***0.86 (0.82-0.90)*** | ***<0.0001*** | ***0.86 (0.82-0.91)*** | ***<0.0001*** | 0.81 (0.68-0.97) | 0.023 |
| **Age 75-79** | ***0.60 (0.56-0.66)*** | ***<0.0001*** | ***0.60 (0.57-0.65)*** | ***<0.0001*** | ***0.55 (0.41-0.75)*** | ***0.0001*** |
| **Age 80-84** | ***0.42 (0.37-0.49)*** | ***<0.0001*** | ***0.43 (0.37-0.49)*** | ***<0.0001*** | ***0.19 (0.07-0.50)*** | ***0.001*** |
| **Age >=85** | ***0.26 (0.19-0.36)*** | ***<0.0001*** | ***0.26 (0.19-0.36)*** | ***<0.0001*** | 0.13 (0.02-1.04) | 0.055 |
| **ADG comorbidity score (continuous variable)** | ***0.994 (0.992-0.996)*** | ***<0.0001*** | ***0.99 (0.992-0.996)*** | ***<0.0001*** | 1.002 (0.994-1.009) | 0.6 |
| **Rurality index (continuous variable)** | 0.999 (0.998-1.001) | 0.633 | 0.999 (0.998-1.0009) | 0.59 | 0.998 (0.993-1.003) | 0.456 |
| **Index Year (continuous variable)** | ***0.97 (0.97-0.98)*** | ***<0.0001*** | ***0.97 (0.97-0.98)*** | ***<0.0001*** | 1.003 (0.96-1.04) | 0.87 |
| **Diabetes (vs. no diabetes)** | ***0.76 (0.65-0.87)*** | ***0.0002*** | ***0.75 (0.66-0.87)*** | ***0.0002*** | 0.61 (0.30-1.25) | 0.18 |
| **PSA (continuous variable)** | - |  | - |  | 1.001 (1.00-1.003) | 0.005 |
| **Statins treatment (reference - no statin treatment)** |  |  |  |  |  |  |
| **Hydrophobic statins** | 0.96 (0.89-1.03) | 0.3 | 0.99 (0.98-1.006) | 0.342 | 0.79 (0.55-1.13) | 0.2 |
| **Hydrophilic statins** | ***0.80 (0.72-0.90)*** | ***0.0002*** | ***0.97 (0.94-0.99)*** | ***0.0002*** | 0.71 (0.53-0.97) | 0.029 |
| All models were also included usage of proton pump inhibitors, alpha blockers, five-alpha-reductase-inhibitors, Chloroquine, Dipyridamole, and glaucoma eye drops  ADG = Johns Hopkins' Aggregated Diagnosis Groups; PSA = Prostate specific antigen | | | | | | |

Table 4 – Cox proportional hazards multivariable regression model predicting the risk of being diagnosed with prostate cancer with medications modeled as ever vs. never and cumulative 6 months usage:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Ever vs. Never** | | **Cumulative 6 months** | | **Ever vs. Never (Only patients with PSA [>2007])** | |
| **Hazard Ratio (95% C.I)** | **P value** | **Hazard Ratio (95% C.I)** | **P value** | **Hazard Ratio (95% C.I)** | **P value** |
| **Age category (reference 66-69)** |  |  |  |  |  |  |
| **Age 70-74** | 1.07 (1.00-1.14) | 0.029 | 1.07 (1.01-1.14) | 0.027 | 1.19 (0.91-1.56) | 0.188 |
| **Age 75-79** | 1.05 (0.99-1.15) | 0.22 | 1.05 (0.97-1.13) | 0.22 | 0.91 (0.59-1.39) | 0.66 |
| **Age 80-84** | ***1.22 (1.08-1.38)*** | ***0.001*** | ***1.22 (1.08-1.38)*** | ***0.001*** | 0.60 (0.22-1.64) | 0.32 |
| **Age >=85** | 1.15 (0.92-1.44) | 0.2 | 1.15 (0.92-1.45) | 0.19 | 1.30 (0.36-4.68) | 0.68 |
| **ADG comorbidity score (continuous variable)** | 0.999 (0.997-1.002) | 0.857 | 0.999 (0.997-1.002) | 0.898 | 1.008 (0.99-1.02) | 0.169 |
| **Rurality index (continuous variable)** | ***1.004 (1.003-1.006)*** | ***<0.0001*** | ***1.004 (1.003-1.006)*** | ***<0.0001*** | 1.003 (0.996-1.011) | 0.31 |
| **Index Year (continuous variable)** | ***0.98 (0.97-0.98)*** | ***<0.0001*** | ***0.98 (0.97-0.98)*** | ***<0.0001*** | ***1.18 (1.10-1.26)*** | ***<0.0001*** |
| **Diabetes (vs. no diabetes)** | 0.90 (0.77-1.06) | 0.22 | 0.90 (0.77-1.06) | 0.22 | 1.39 (0.67-2.87) | 0.371 |
| **PSA (continuous variable)** | - |  | - |  | ***1.002 (1.001-1.004)*** | ***<0.0001*** |
| **Statin treatment (reference - no statin treatment)** |  |  |  |  |  |  |
| **Hydrophobic statins** | 0.97 (0.89-1.06) | 0.544 | 0.99 (0.98-1.00) | 0.299 | 0.71 (0.40-1.23) | 0.22 |
| **Hydrophilic statins** | ***0.82 (0.73-0.94)*** | ***0.003*** | 0.97 (0.95-0.99) | 0.017 | 0.89 (0.59-1.33) | 0.56 |
| All models were also included usage of proton pump inhibitors, alpha blockers, five-alpha-reductase-inhibitors, Chloroquine, Dipyridamole, and glaucoma eye drops  ADG = Johns Hopkins' Aggregated Diagnosis Groups; PSA = Prostate specific antigen | | | | | | |

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