Figure 1 – Patient flowchart:

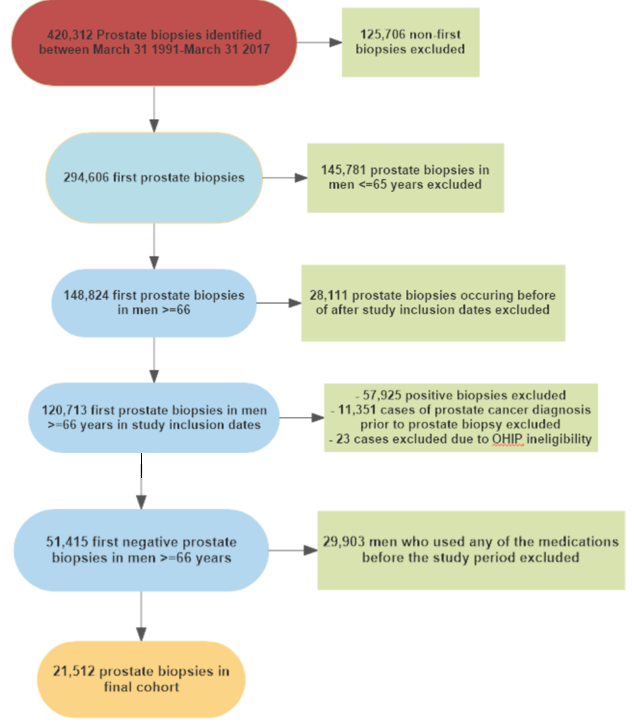


Figure 2 - Use of medications among study patients:

Table 1 – Basic Demographic characteristics of all patients:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***All patients*** | ***Age 66-69*** | ***Age 70-74*** | ***Age 75-79*** | ***Age 80-84*** | ***Age >=85*** | ***p Value*** |
| Number of men, (%) | 21,512 (100%) | 8,492 (39.5%) | 7,497 (34.8%) | 3,722 (17.3%) | 1,336 (6.2%) | 465 (2.2%) | - |
| Time-period, n (%)  1994-2000  2001-2007  2008-2014 | 12,131 (56.4%)  6,634 (30.8%)  2,747 (12.8%) | 4,281 (50.4%)  2,777 (32.7%)  1,434 (16.9%) | 4,317 (57.6%)  2,316 (30.9%)  864 (11.5%) | 2,360 (63.4%)  1,037 (27.9%)  325 (8.7%) | 863 (64.6%)  392 (29.3%)  81 (6.1%) | 310 (66.7%)  112 (24.1%)  43 (9.2%) | <0.001 |
| Mean ADG score, (SD) | 18.97 (11.62) | 16.85 (10.9) | 18.66 (11.28) | 21.44 (11.97) | 24.33 (12.09) | 27.49 (12.95) | <0.001 |
| Patients with medically-treated Diabetes, n (%) | 2,331 (10.8%) | 1,051 (12.4%) | 833 (11.1%) | 345 (9.3%) | 81 (6.1%) | 21 (4.5%) | <0.001 |
| 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) | 0.216 |
| Income quintile, n (%)  1  2  3  4  5  Not available | 3,439 (16%)  4,167 (19.4%)  4,289 (19.9%)  4,356 (20.2%)  5,164 (24%)  97 (0.5%) | 1,260 (14.8%)  1,570 (18.5%)  1,655 (19.5%)  1,807 (21.3%)  2,165 (25.5%)  35 (0.4%) | 1,157 (15.4%)  1,470 (19.6%)  1,498 (20.0%)  1,500 (20.0%)  1,833 (24.4%)  39 (0.5%) | 686 (18.4%)  751 (20.2%)  759 (20.4%)  706 (19.0%)  805 (21.6%)  15 (0.4%) | 242 (18.1%)  277 (20.7%)  283 (21.2%)  260 (19.5%)  268 (20.1%)  6 (0.4%) | 94 (20.2%)  99 (21.3%)  94 (20.2%)  83 (17.8%)  93 (20.0%)  2 (0.4%) | <0.001 |

Table 2 – 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** | **P value** | **Cumulative 6 months** | **P value** | **Ever vs. Never (Only patients with PSA [>2007])** | **P value** |
| **Hazard Ratio (95% C.I)** |  | **Hazard Ratio (95% C.I)** |  | **Hazard Ratio (95% C.I)** |  |
| **Age category 70-74 (reference 66-69)** | 1.07 (1.006-1.14) | 0.029 | 1.07 (1.007-1.14) | 0.027 | 1.19 (0.91-1.557) | 0.188 |
| **Age category 75-79 (reference 66-69)** | 1.05 (0.998-1.15) | 0.22 | 1.05 (0.969-1.13) | 0.22 | 0.91 (0.59-1.39) | 0.66 |
| **Age category 80-84 (reference 66-69)** | ***1.22 (1.08-1.38)*** | ***0.001*** | ***1.22 (1.08-1.38)*** | ***0.001*** | 0.6 (0.22-1.64) | 0.32 |
| **Age category 85-89 (reference 66-69)** | 1.15 (0.92-1.44) | 0.2 | 1.15 (0.92-1.45) | 0.19 | 1.3 (0.36-4.68) | 0.68 |
| **ADG comorbidity score** | 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** | ***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** | ***0.98 (0.974-0.985)*** | ***<0.0001*** | ***0.979 (0.973-0.985)*** | ***<0.0001*** | ***1.18 (1.1-1.26)*** | ***<0.0001*** |
| **Diabetes** | 0.9 (0.775-1.06) | 0.22 | 0.9 (0.77-1.06) | 0.22 | 1.39 (0.674-2.87) | 0.371 |
| **PSA** | - |  | - |  | ***1.002 (1.001-1.004)*** | ***<0.0001*** |
| **Hydrophobic statins** | 0.972 (0.889-1.06) | 0.544 | 0.993 (0.982-1.005) | 0.299 | 0.71 (0.4-1.233) | 0.22 |
| ***Hydrophilic statins*** | ***0.82 (0.727-0.939)*** | ***0.003*** | 0.973 (0.951-0.995) | 0.017 | 0.886 (0.586-1.33) | 0.56 |

Table 3 - 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** | **P value** | **Cumulative 6 months** | **P value** |
| **Hazard Ratio (95% C.I)** |  | **Hazard Ratio (95% C.I)** |  |
| **Age category 70-74 (reference 66-69)** | ***1.68 (1.34-1.98)*** | ***<0.0001*** | ***1.67 (1.38-2.02)*** | ***<0.0001*** |
| **Age category 75-79 (reference 66-69)** | ***3.05 (2.46-3.77)*** | ***<0.0001*** | ***3.15 (2.55-3.9)*** | ***<0.0001*** |
| **Age category 80-84 (reference 66-69)** | ***5.25 (3.98-6.93)*** | ***<0.0001*** | ***5.51 (4.18-7.2)*** | ***<0.0001*** |
| **Age category 85-89 (reference 66-69)** | ***9.79 (6.27-15.28)*** | ***<0.0001*** | ***10.14 (6.5-15.8)*** | ***<0.0001*** |
| **ADG score** | 1.005 (0.998-1.01) | 0.1 | 1.006 (0.999-1.01) | 0.07 |
| **Rurality index** | 1.004 (1.0009-1.008) | 0.01 | 1.004 (1.0009-1.008) | 0.01 |
| **Index Year** | ***0.91 (0.89-0.94)*** | ***<0.0001*** | ***0.92 (0.9-0.95)*** | ***<0.0001*** |
| **Diabetes** | 1.36 (1.07-1.72) | 0.01 | 1.35 (1.072-1.72) | 0.011 |
| **Radiotherapy** | 1.29 (0.89-1.87) | 0.17 | 1.26 (0.87-1.83) | 0.21 |
| **Radical Prostatectomy** | 0.939 (0.62-1.41) | 0.76 | 0.930 (0.618-1.41) | 0.75 |
| **Primary androgen deprivation therapy** | 1.01 (0.787-1.3) | 0.91 | 1.02 (0.79-1.32) | 0.84 |
| **Hydrophobic statins** | 0.828 (0.696-0.984) | 0.032 | 0.983 (0.968-0.999) | 0.046 |
| ***Hydrophilic statins*** | ***0.676 (0.525-0.871)*** | ***0.0024*** | 0.957 (0.92-0.99) | 0.018 |
| All models were also adjusted for 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 having an additional prostate biopsy with medications modeled as ever vs. never and cumulative 6 months usage:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Ever vs. Never** | **P value** | **Cumulative 6 months** | **P value** | **Ever vs. Never (Only patients with PSA [>2007])** | **P value** |
| **Hazard Ratio (95% C.I)** |  | **Hazard Ratio (95% C.I)** |  | **Hazard Ratio (95% C.I)** |  |
| **Age category 70-74 (reference 66-69)** | ***0.863 (0.82-0.9)*** | ***<0.0001*** | ***0.865 (0.822-0.909)*** | ***<0.0001*** | 0.815 (0.68-0.97) | 0.023 |
| **Age category 75-79 (reference 66-69)** | ***0.6 (0.565-0.665)*** | ***<0.0001*** | ***0.6 (0.566-0.65)*** | ***<0.0001*** | ***0.55 (0.411-0.75)*** | ***0.0001*** |
| **Age category 80-84 (reference 66-69)** | ***0.425 (0.371-0.488)*** | ***<0.0001*** | ***0.428 (0.374-0.49)*** | ***<0.0001*** | ***0.19 (0.07-0.5)*** | ***0.001*** |
| **Age category 85-89 (reference 66-69)** | ***0.26 (0.19-0.36)*** | ***<0.0001*** | ***0.265 (0.193-0.364)*** | ***<0.0001*** | 0.13 (0.017-1.04) | 0.055 |
| **ADG comorbidity score** | ***0.994 (0.992-0.996)*** | ***<0.0001*** | ***0.994 (0.992-0.996)*** | ***<0.0001*** | 1.002 (0.994-1.009) | 0.6 |
| **Rurality index** | 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** | ***0.974 (0.969-0.978)*** | ***<0.0001*** | ***0.978 (0.973-0.983)*** | ***<0.0001*** | 1.003 (0.961-1.04) | 0.87 |
| **Diabetes** | ***0.756 (0.646-0.874)*** | ***0.0002*** | ***0.755 (0.649-0.879)*** | ***0.0002*** | 0.61 (0.3-1.255) | 0.18 |
| **PSA** | - |  | - |  | 1.001 (1-1.003) | 0.005 |
| **Hydrophobic statins** | 0.959 (0.886-1.03) | 0.3 | 0.993 (0.98-1.006) | 0.342 | 0.79 (0.554-1.13) | 0.2 |
| ***Hydrophilic statins*** | ***0.8 (0.72-0.9)*** | ***0.0002*** | ***0.968 (0.944-0.992)*** | ***0.0002*** | 0.71 (0.529-0.968) | 0.029 |
| All models were also adjusted for 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 | | | | | | |

**Supplemental table 1 – Data sources used from the Institute of clinical evaluative sciences:**

|  |  |  |
| --- | --- | --- |
| Database | Used for | Reference |
| Ontario Cancer Registry (OCR) | identifying incident prostate cancer cases with accuracy > 93% | 1.E. J. Holowaty VM, G. Lee, N. Chong and D. Dale, Cancer Bureau, Health Canada. A Reabstraction Study to Estimate the Completeness and Accuracy of Data Elements in the Ontario Cancer Registry Final Report Contract H4078-3-C098, Ottawa 1996  2. Robles SC, Marrett LD, Aileen Clarke E, Risch HA. An application of capture-recapture methods to the estimation of completeness of cancer registration. Journal of Clinical Epidemiology 1988; 41(5): 495-501. |
| Ontario Health insurance program (OHIP) | Tracks claims paid to physicians, laboratories, and out-of-province providers | Chan B. Supply of physicians' services in Ontario. Hospital quarterly 1999; 3(2): 17 |
| Registered persons database (RPDB) | Contains information on persons registered under OHIP and persons who are eligible for the Ontario Drug Program (over 65 years old) | Ontario Ministry of Health and Long-Term Care  Health System Information Management and Investment Division. Health Analyst’s Toolkit. Health Analytics Branch Winter 2012 |
| Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) | Contains in-patient hospitalization data | Clarke E ML, Kreiger N. Cancer registration: principles and methods. Lyon, France: IARS Scientific Publications; 1991. |
| Ontario Drug Benefit database (ODB) | Includes data on all drug prescriptions for patients older than 65 in Ontario | Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. The Canadian journal of clinical pharmacology = Journal canadien de pharmacologie clinique 2003; 10(2): 67-71. |
| Ontario laboratory information system (OLIS) | Contains the results for approximately 95% of all laboratory tests conducted on patients in Ontario | ICES. The value of Ontario’s electronic health data infrastructure - A brief report from the perspective of the Institute for Clinical Evaluative Sciences. 2016. |
| Ontario office of the Registrar General (ORG) | Includes individual-level vital statistics and death data |  |

Supplemental table 2 – Source databased and Ontario Heath Insurance Plan (OHIP) database and the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) codes used to identify disease state and procedures:

|  |  |
| --- | --- |
| **Procedure** | **Code** |
| **Ontario Health Insurance Plan Database** | |
| Prostate biopsy | Z712, Z713, S644, E780 |
| Pelvic/abdominal ultrasound | J128, J135, J138, J149, J162, J180 |
| Radiation therapy for prostate cancer (pelvis-specific) | X336, X310, X311,X312, X313, X322 |
| Brachytherapy | S640 till 2007, afterwards X323, X324, X325 |
| Implantation of hormone pellets | G342 |
| **Canadian Institute of Health Information Discharge Abstract Database** | |
| Bilateral orchiectomy | CCP Code: 74.31; CCI Code: 1QM89 |
| Radical prostatectomy | CCP: 72.4, CCI: 1QT91 |

Supplement table 3 - Cox proportional hazards multivariable regression model predicting the risk of being diagnosed with prostate cancer with both groups of statins combined and medications modeled as ever vs. never and cumulative 6 months usage:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Ever vs. Never** | **P value** | **Cumulative 6 months** | **P value** |
|  | **Hazard Ratio (95% C.I)** |  | **Hazard Ratio (95% C.I)** |  |
| **Age category 70-74 (reference 66-69)** | 1.07 (1.005-1.14) | 0.032 | 1.072 (1.007-1.14) | 0.028 |
| **Age category 75-79 (reference 66-69)** | 1.04 (0.968-1.13) | 0.239 | 1.05 (0.969-1.13) | 0.22 |
| **Age category 80-84 (reference 66-69)** | ***1.22 (1.08-1.38)*** | ***0.001*** | ***1.22 (1.08-1.38)*** | ***0.0009*** |
| **Age category 85-89 (reference 66-69)** | 1.15 (0.925-1.45) | 0.199 | 1.16 (0.927-1.45) | 0.19 |
| **ADG comorbidity score** | 0.999 (0.997-1.002) | 0.877 | 0.999 (0.997-1.002) | 0.88 |
| **Rurality index** | ***1.004 (1.003-1.006)*** | ***<0.0001*** | ***1.004 (1.003-1.006)*** | ***<0.0001*** |
| **Index Year** | ***0.979 (0.973-0.98)*** | ***<0.0001*** | ***0.979 (0.973-0.985)*** | ***<0.0001*** |
| **Statins combined** | 0.933 (0.858-1.01) | 0.1 | 0.989 (0.978-0.999) | 0.046 |
| All models were also adjusted for usage of proton pump inhibitors, alpha blockers, five-alpha-reductase-inhibitors, Chloroquine, Dipyridamole, metformin, Insulin, sulphonyl urea, thiazolidinediones, and glaucoma eye drops  ADG = Johns Hopkins' Aggregated Diagnosis Groups | | | | |

Supplement table 4 - Cox proportional hazards multivariable regression model predicting the risk of being diagnosed with prostate cancer incorporating the median dose of statin groups with medications modeled as ever vs. never usage:

|  |  |  |
| --- | --- | --- |
|  | **Hazard Ratio (95% C.I)** | **P value** |
| **Age category 70-74 (reference 66-69)** | 1.07 (1.005-1.14) | 0.03 |
| **Age category 75-79 (reference 66-69)** | 1.048 (0.967-1.137) | 0.249 |
| **Age category 80-84 (reference 66-69)** | ***1.22 (1.082-1.38)*** | ***0.001*** |
| **Age category 85-89 (reference 66-69)** | 1.15 (0.92-1.45) | 0.2 |
| **ADG comorbidity score** | 0.999 (0.997-1.002) | 0.87 |
| **Rurality index** | ***1.0049 (1.003-1.006)*** | ***<0.0001*** |
| **Index Year** | ***0.98 (0.974-0.986)*** | ***<0.0001*** |
| **Hydrophobic statins dose < median** | 0.998 (0.896-1.11) | 0.984 |
| **Hydrophobic statins dose > median** | 0.935 (0.819-1.068) | 0.32 |
| **Hydrophilic statins dose < Median** | 0.857 (0.73-1.006) | 0.059 |
| ***Hydrophilic statins dose > Median*** | 0.791 (0.651-0.963) | 0.019 |
| All models were also adjusted for usage of proton pump inhibitors, alpha blockers, five-alpha-reductase-inhibitors, Chloroquine, Dipyridamole, metformin, Insulin, sulphonyl urea, thiazolidinediones, and glaucoma eye drops  ADG = Johns Hopkins' Aggregated Diagnosis Groups | | |

Supplement table 5 - Cox proportional hazards multivariable regression model predicting the risk of being diagnosed with prostate cancer incorporating the statin interactions with metformin and dipyridamole with medications modeled as ever vs. never usage:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Metformin\*Statins** | **P value** | **Dipyridamole\*Statins** | **P value** |
| **Hazard Ratio (95% C.I)** |  | **Hazard Ratio (95% C.I)** |  |
| **Age category 70-74 (reference 66-69)** | 1.07 (1.005-1.14) | 0.032 | 1.07 (1.005-1.14) | 0.032 |
| **Age category 75-79 (reference 66-69)** | 1.04 (0.967-1.13) | 0.24 | 1.04 (0.967-1.13) | 0.24 |
| **Age category 80-84 (reference 66-69)** | ***1.22 (1.08-1.38)*** | ***0.001*** | ***1.22 (1.08-1.38)*** | ***0.001*** |
| **Age category 85-89 (reference 66-69)** | 1.15 (0923-1.44) | 0.203 | 1.15 (0.924-1.44) | 0.203 |
| **ADG comorbidity score** | 0.999 (0.997-1.002) | 0.87 | 0.999 (0.997-1.002) | 0.87 |
| **Rurality index** | ***1.004 (1.003-1.006)*** | ***<0.0001*** | ***1.004 (1.003-1.006)*** | ***<0.0001*** |
| **Index Year** | ***0.98 (0.974-0.986)*** | ***<0.0001*** | ***0.98 (0.974-0.986)*** | ***<0.0001*** |
| **Hydrophobic statins** | 0.97 (0.885-1.065) | 0.534 | 0.977 (0.892-1.069) | 0.61 |
| **Hydrophilic statins** | 0.843 (0.738-0.96) | 0.012 | 0.833 (0.732-0.948) | 0.0058 |
| **Metformin** | 0.792 (0.592-1.06) | 0.11 | 0.789 (0.644-0.968) | 0.02 |
| **Dipyridamole** | 1.17 (0.8-1.69) | 0.4 | 1.29 (0.69-2.44) | 0.41 |
| **Hydrophobic statins\*Metformin** | 1.05 (0.729-1.52) | 0.779 | - | - |
| **Hydrophilic statins\*Metformin** | 0.872 (0.549-1.38) | 0.561 | - | - |
| **Hydrophobic statins\*Dipyridamole** | - | - | 0.87 (0.4-1.84) | 0.718 |
| **Hydrophilic statins\*Dipyridamole** | - | - | 0.926 (0.387-2.21) | 0.863 |
| All models were also adjusted for usage of proton pump inhibitors, alpha blockers, five-alpha-reductase-inhibitors, Chloroquine, Insulin, sulphonyl urea, thiazolidinediones, and glaucoma eye drops  ADG = Johns Hopkins' Aggregated Diagnosis Groups | | | | |

Supplement table 6 - Cox proportional hazards multivariable regression model predicting the risk of prostate cancer specific death with both groups of statins combined and medications modeled as ever vs. never usage:

|  |  |  |
| --- | --- | --- |
|  | **Hazard Ratio (95% C.I)** | **P value** |
| **Age category 70-74 (reference 66-69)** | ***1.38 (1.13-1.68)*** | ***0.001*** |
| **Age category 75-79 (reference 66-69)** | ***2.41 (1.93-3.01)*** | ***<0.0001*** |
| **Age category 80-84 (reference 66-69)** | ***4.16 (3.11-5.57)*** | ***<0.0001*** |
| **Age category 85-89 (reference 66-69)** | ***6.89 (4.37-10.85)*** | ***<0.0001*** |
| **ADG comorbidity score** | 1.004 (0.99-1.01) | 0.189 |
| **Rurality index** | 1.004 (1.001-1.008) | 0.0138 |
| **Index Year** | ***0.9 (0.878-0.92)*** | ***<0.0001*** |
| **Radiotherapy** | ***1.86 (1.52-2.27)*** | ***<0.0001*** |
| **Radical prostatectomy** | ***0.47 (0.31-0.71)*** | ***0.0004*** |
| **Androgen deprivation therapy** | ***4.36 (3.56-5.33)*** | ***<0.0001*** |
| ***Statins combined*** | ***0.76 (0.64-0.90)*** | ***0.0018*** |
| All models were also adjusted for usage of proton pump inhibitors, alpha blockers, five-alpha-reductase-inhibitors, Chloroquine, Dipyridamole, metformin, Insulin, sulphonyl urea, thiazolidinediones, and glaucoma eye drops  ADG = Johns Hopkins' Aggregated Diagnosis Groups | | |

Supplement table 7 - Negative control model - Cox proportional hazards multivariable regression model predicting the risk of being diagnosed with presbyopia with medications modeled as ever vs. never usage:

|  |  |  |
| --- | --- | --- |
|  | **Hazard Ratio (95% C.I)** | **P value** |
| **Age category 70-74 (reference 66-69)** | 0.96 (0.89-1.05) | 0.46 |
| **Age category 75-79 (reference 66-69)** | 0.99 (0.89-1.099) | 0.88 |
| **Age category 80-84 (reference 66-69)** | 0.84 (0.71-1.001) | 0.052 |
| **Age category 85-89 (reference 66-69)** | 0.788 (0.586-1.06) | 0.11 |
| **ADG comorbidity score** | ***1.005 (1.002-1.009)*** | ***0.0003*** |
| **Rurality index** | ***0.982 (0.98-0.985)*** | ***<0.0001*** |
| **Index Year** | ***0.857 (0.849-0.866)*** | ***<0.0001*** |
| **Diabetes** | 1.01 (0.8-1.27) | 0.91 |
| **Hydrophobic statins** | 0.95 (0.828-1.09) | 0.5 |
| **Hydrophilic statins** | 1.09 (0.897-1.32) | 0.38 |
| All models were also adjusted for usage of proton pump inhibitors, alpha blockers, five-alpha-reductase-inhibitors, Chloroquine, dipyridamole, and glaucoma eye drops  ADG = Johns Hopkins' Aggregated Diagnosis Groups | | |

Supplemental Figure 1 –Prostate cancer diagnosis, prostate cancer-specific death, and all-cause mortality stratified by age:

Supplemental Figure 2 – Prostate cancer treatment modalities stratified by age:

ADT = Androgen deprivation therapy; AS = Active surveillance; WW = Watchful waiting

Supplemental Figure 3 - Additional prostate biopsies by age: