Table 1 – Basic demographic and clinical data:

|  |  |  |
| --- | --- | --- |
|  | **Treated with Metformin** | **Not treated with metformin** |
| **Number of patients (%)** | 2036 (87.3%) | 296 (12.7%) |
| **Age category, n (%) (years)** |  | |
| **66-69** | 957 (47%) | 95 (32.1%) |
| **70-74** | 731 (35.9%) | 102 (34.5%) |
| **75-79** | 277 (13.6%) | 68 (23%) |
| **80-84** | 57 (2.8%) | 24 (8.1%) |
| **>=85** | 14 (0.7%) | 7 (2.4%) |
| **Time period, n (%)** |  | |
| **1994-2000** | 1315 (64.6%) | 230 (77.7%) |
| **2001-2007** | 598 (29.4%) | 63 (21.3%) |
| **2008-2014** | 123 (6%) | 3 (1%) |
| **Rurality index, mean (SD)** | 12.23 (18.59) | 10.66 (15.73) |
| **Income quintile, n (%)** |  | |
| **1** | 368 (18.1%) | 60 (20.3%) |
| **2** | 422 (20.7%) | 64 (21.6%) |
| **3** | 427 (21%) | 59 (19.9%) |
| **4** | 387 (19%) | 58 (19.6%) |
| **5** | 426 (20.9%) | 55 (18.6%) |
| **Not available** | 6 (0.3%) | 0 |
| **Mean ADG score (SD)** | 18.96 (11.40) | 22.2 (12.90) |
| **Mean Follow-up time (years) (SD)** | 11.06 (6.16) | 8.48 (5.65) |

ADG = Johns Hopkins Aggregated Diagnosis Groups

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:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Diabetic only ever VS. never** | | **Diabetic only Cumulative drug usage for 6 months** | |
|  | **HR (95% C.I)** | **p value** | **HR (95% C.I)** | **p value** |
| **Age category (66-69 years reference)** |  | | | |
| **70-74 years** | 0.95 (0.79-1.13) | 0.55 | 0.94 (0.79-1.13) | 0.52 |
| **75-89 years** | 1.09 (0.87-1.38) | 0.44 | 1.09 (0.86-1.37) | 0.45 |
| **80-84 years** | 1.60 (1.08-2.35) | 0.02 | 1.60 (1.08-2.35) | 0.02 |
| **>=85 years** | 1.59 (0.7-3.59) | 0.26 | 1.52 (0.67-3.42) | 0.31 |
| **ADG comorbidity score (continuous)** | 0.999 (0.993-1.006) | 0.95 | 0.999 (0.992-1.006) | 0.92 |
| **Rurality index (continuous)** | 1.002 (0.998-1.006) | 0.32 | 1.002 (0.998-1.006) | 0.27 |
| **Index Year (continuous)** | 1.007 (0.987-1.020) | 0.47 | 0.99 (0.98-1.02) | 0.78 |
| **Glaucoma eye drops (yes vs. no)** | 0.53 (0.28-1.01) | 0.53 | 0.74 (0.50-1.08) | 0.64 |
| **5ARI (yes vs. no)** | 0.64 (0.44-0.95) | 0.03 | 0.96 (0.896-1.02) | 0.22 |
| **Alpha blockers (yes vs. no)** | 1.05 (0.83-1.33) | 0.67 | 0.99 (0.95-1.03) | 0.64 |
| **Hydrophobic statins (yes vs. no)** | 1.06 (0.86-1.32) | 0.56 | 0.999 (0.973-1.026) | 0.96 |
| **Hydrophilic statins (yes vs. no)** | 0.77 (0.568-1.06) | 0.11 | 0.97 (0.92-1.02) | 0.18 |
| **Insulin (yes vs. no)** | 0.599 (0.26-1.36) | 0.22 | 1.03 (0.89-1.2) | 0.66 |
| **Metformin** **(yes vs. no)** | 0.69 (0.54-0.88) | 0.003 | 0.98 (0.94-1.01) | 0.27 |
| **Sulphonylurea (yes vs. no)** | 1.22 (0.96-1.55) | 0.10 | 1.02 (0.99-1.06) | 0.11 |
| **Thiazolidinediones (yes vs. no)** | 0.63 (0.23-1.72) | 0.37 | 0.85 (0.64-1.11) | 0.24 |
| **Pantoprazole (yes vs. no)** | 1.03 (0.69-1.54) | 0.87 | 1.069 (1.001-1.140) | 0.05 |
| **All other PPIs (yes vs. no)** | 0.87 (0.66-1.14) | 0.33 | 0.97 (0.91-1.022) | 0.24 |
| **Chloroquine (yes vs. no)** | 1.35 (0.55-3.30) | 0.50 | 1.23 (0.79-1.93) | 0.36 |
| **Dipyridamole (yes vs. no)** | 1.2 (0.45-3.25) | 0.71 | 1.04 (0.87-1.25) | 0.62 |

5ARI = Five alpha reductase inhibitors, ADG = Johns Hopkins Aggregated Diagnosis Groups; PPIs = Proton pump inhibitors

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Diabetic only ever VS. never** | | **Diabetic only Cumulative drug usage for 6 months** | |
|  | **HR (95% C.I)** | **p value** | **HR (95% C.I)** | **p value** |
| **Age category (Reference 66-69 years)** |  | | | |
| **70-74 years** | 0.80 (0.70-0.93) | 0.003 | 0.80 (0.69-0.92) | 0.002 |
| **75-79 years** | 0.66 (0.53-0.82) | 0.0001 | 0.65 (0.52-0.81) | <0.0001 |
| **80-84 years** | 0.46 (0.28-0.74) | 0.001 | 0.47 (0.29-0.78) | 0.003 |
| **>=85 years** | 0.36 (0.11-1.12) | 0.78 | 0.36 (0.11-1.11) | 0.08 |
| **ADG comorbidity score (continuous)** | 0.996 (0.990-1.002) | 0.26 | 0.996 (0.990-1.002) | 0.26 |
| **Rurality index (continuous)** | 0.998 (0.994-1.001) | 0.31 | 0.998 (0.994-1.001) | 0.33 |
| **Index Year (continuous)** | 0.989 (0.971-1.006) | 0.22 | 0.985 (0.968-1.001) | 0.07 |
| **Glaucoma eye drops (yes vs. no)** | 0.70 (0.40-1.20) | 0.19 | 0.60 (0.43-1.120) | 0.13 |
| **5ARI (yes vs. no)** | 0.999 (0.698-1.430) | 0.99 | 0.897 (0.800-1.004) | 0.06 |
| **Alpha blockers (yes vs. no)** | 1.50 (1.10-1.65) | 0.003 | 1.03(0.98-1.07) | 0.21 |
| **Hydrophobic statins (yes vs. no)** | 1.01 (0.84-1.22) | 0.90 | 1.02 (0.99-1.05) | 0.22 |
| **Hydrophilic statins (yes vs. no)** | 0.79 (0.59-1.06) | 0.12 | 1.005 (0.950-1.060) | 0.84 |
| **Insulin (yes vs. no)** | 0.89 (0.41-1.89) | 0.76 | 0.95 (0.71-1.26) | 0.72 |
| **Metformin** **(yes vs. no)** | 0.62 (0.49-0.78) | <0.0001 | 0.95 (0.91-0.99) | 0.02 |
| **Sulphonylurea (yes vs. no)** | 0.99 (0.79-1.24) | 0.93 | 1.007 (0.960-1.052) | 0.76 |
| **Thiazolidinediones (yes vs. no)** | 0.84v(0.30-2.29) | 0.73 | 0.90 (0.67-1.19) | 0.47 |
| **Pantoprazole (yes vs. no)** | 1.19 (0.80-1.77) | 0.38 | 1.00 (0.94-1.170) | 0.38 |
| **All other PPIs (yes vs. no)** | 0.85 (0.65-1.11) | 0.24 | 0.918 (0.840-1.001) | 0.06 |
| **Chloroquine (yes vs. no)** | 0.66 (0.21-2.07) | 0.47 | 0.77 (0.21-2.80) | 0.70 |
| **Dipyridamole (yes vs. no)** | 1.08 (0.40-2.91) | 0.87 | 0.50 (0.12-2.11) | 0.34 |

5ARI = Five alpha reductase inhibitors, ADG = Johns Hopkins Aggregated Diagnosis Groups; PPIs = Proton pump inhibitors

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Diabetic only ever VS. never** | | **Diabetic only Cumulative drug usage for 6 months** | |
|  | **HR (95% C.I)** | **p value** | **HR (95% C.I)** | **p value** |
| **Age category (66-69 years reference)** |  | | | |
| **70-74 years** | 1.64 (1.31-2.05) | <0.0001 | 1.65 (1.32-2.07) | <0.0001 |
| **75-89 years** | 2.69 (2.04-3.57) | <0.0001 | 2.76 (2.08-3.64) | <0.0001 |
| **80-84 years** | 2.02 (1.25-3.26) | 0.003 | 2.06 (1.28-3.32) | 0.002 |
| **>=85 years** | 1.69 (0.59-5.36) | 0.37 | 1.70 (0.53-5.37) | 0.36 |
| **ADG comorbidity score (continuous)** | 1.006 (0.998-1.010) | 0.12 | 1.006 (0.998-1.010) | 0.13 |
| **Rurality index (continuous)** | 1.002 (0.997-1.007) | 0.43 | 1.001 (0.996-1.006) | 0.51 |
| **Index Year (continuous)** | 0.960 (0.930-0.996) | 0.03 | 0.96 (0.93-0.99) | 0.009 |
| **Glaucoma eye drops (yes vs. no)** | 0.84 (0.44-1.60) | 0.60 | 0.94 (0.80-1.11) | 0.47 |
| **5ARI (yes vs. no)** | 1.38 (0.90-2.11) | 0.13 | 1.05 (0.98-1.13) | 0.12 |
| **Alpha blockers (yes vs. no)** | 1.13 (0.87-1.48) | 0.34 | 1.006 (0.966-1.040) | 0.77 |
| **Hydrophobic statins (yes vs. no)** | 0.98 (0.76-1.27) | 0.89 | 0.98 (0.96-1.01) | 0.32 |
| **Hydrophilic statins (yes vs. no)** | 0.99 (0.70-1.39) | 0.94 | 1.006 (0.960-1.050) | 0.77 |
| **Insulin (yes vs. no)** | 0.81 (0.37-1.81) | 0.61 | 0.99 (0.90-1.09) | 0.86 |
| **Metformin** **(yes vs. no)** | 0.72 (0.54-0.96) | 0.03 | 0.99 (0.96-1.03) | 0.97 |
| **Sulphonylurea (yes vs. no)** | 1.10 (0.84-1.45) | 0.48 | 0.997 (0.961-1.030) | 0.88 |
| **Thiazolidinediones (yes vs. no)** | 0.84 (0.33-2.12) | 0.71 | 0.96 (0.75-1.22) | 0.76 |
| **Pantoprazole (yes vs. no)** | 1.23 (0.81-1.87) | 0.49 | 1.04 (0.98-1.11) | 0.12 |
| **All other PPIs (yes vs. no)** | 0.90 (0.66-1.22) | 0.32 | 0.998 (0.947-1.050) | 0.96 |
| **Chloroquine (yes vs. no)** | 1.30 (0.49-3.63) | 0.57 | 1.24 (0.76-2.03) | 0.37 |
| **Dipyridamole (yes vs. no)** | 1.17 (0.47-2.90) | 0.73 | 0.97 (0.81-1.17) | 0.82 |

5ARI = Five alpha reductase inhibitors, ADG = Johns Hopkins Aggregated Diagnosis Groups; PPIs = Proton pump inhibitors

Figure 1 – Mean cumulative use (months) of medications stratified by age:

**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 |

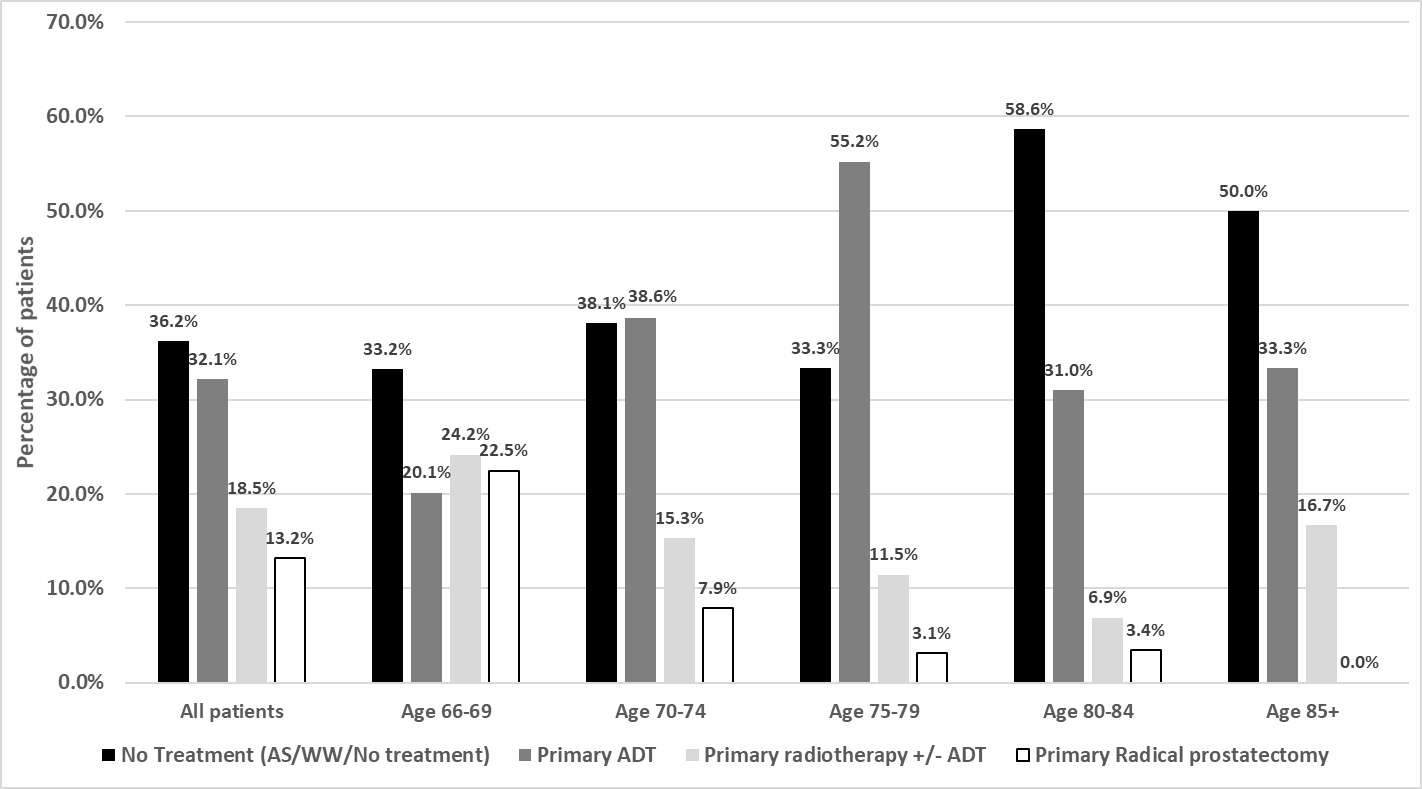
Supplemental Table 3 - Negative control model - Cox proportional hazards multivariable regression model predicting the risk of being diagnosed with presbyopia with medications modeled as ever vs. never:

|  |  |  |
| --- | --- | --- |
|  | **Diabetic only ever VS. never** | |
|  | **HR (95% C.I)** | **p value** |
| **Age category (66-69 years reference)** |  | |
| **70-74 years** | 0.97 (0.89-1.05) | 0.46 |
| **75-89 years** | 0.99 (0.89-1.10 | 0.87 |
| **80-84 years** | 0.847 (0.717-1.001) | 0.051 |
| **>=85 years** | 0.78 (0.58-1.06) | 0.11 |
| **ADG comorbidity score (continuous)** | 1.005 (1.002-1.009) | 0.0003 |
| **Rurality index (continuous)** | 0.982 (0.9801-0.985) | <0.0001 |
| **Index Year (continuous)** | 0.850 (0.849-0.867) | <0.0001 |
| **Glaucoma eye drops (yes vs. no)** | 1.26 (0.99-1.62) | 0.06 |
| **5ARI (yes vs. no)** | 1.21 (0.97-1.52) | 0.08 |
| **Alpha blockers (yes vs. no)** | 1.19 (0.99-1.35) | 0.06 |
| **Hydrophobic statins (yes vs. no)** | 0.96 (0.83-1.10) | 0.54 |
| **Hydrophilic statins (yes vs. no)** | 1.096 (0.900-1.334) | 0.36 |
| **Insulin (yes vs. no)** | 0.48 (0.11-1.98) | 0.31 |
| **Metformin** **(yes vs. no)** | 0.97(0.70-1.31) | 0.82 |
| **Sulphonylurea (yes vs. no)** | 1.07(0.78-1.49) | 0.65 |
| **Thiazolidinediones (yes vs. no)** | 0.47 (0.06-3.46) | 0.46 |
| **Pantoprazole (yes vs. no)** | 1.10 (0.85-1.43) | 0.45 |
| **All other PPIs (yes vs. no)** | 1.02 (0.87-1.19) | 0.79 |
| **Chloroquine (yes vs. no)** | 1.49 (0.88-2.54) | 0.13 |
| **Dipyridamole (yes vs. no)** | 0.93 (0.46-1.87) | 0.84 |

5ARI = Five alpha reductase inhibitors, ADG = Johns Hopkins Aggregated Diagnosis Groups; PPIs = Proton pump inhibitors

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

Supplemental Figure 2 – The various prostate cancer treatments stratified by age:



ADT = Androgen Deprivation Therapy; AS = Active Surveillance; WW = Watchful Waiting