Materials and Methods:

Study Cohort:

A population-based retrospective cohort study of Ontarian men aged 66 years or older between the years 1994 and 2014 was conducted. The inclusion criteria for the study was that the men must not have taken any of the medications of interest before the age of 66 years and must have had a prostate cancer biopsy test taken, with a negative result. Note that men who did not take a biopsy test were not included in the study. Hence, only people who had cause for their doctor to prescribe a biopsy test, and subsequently had a negative result, were included in the study. As such, our population of study was a high risk population for prostate cancer. All the data were obtained from the ICES Data Repository. The time origin of the cohort was the first negative prostate biopsy after age 66, with subsequent follow-up for prostate cancer incidence until the end of the coverage period of administrative data records.

Statistical Methodology:

We were interested in estimating the effects of using cardiovascular medications on prostate cancer incidence hazard. To estimate the effects of medication exposure, a multivariable Cox proportional hazard regression model with time-dependent exposure was used. The exposure to each medication was modeled as a time-dependent status indicator, i.e. as a time-dependent binary variable with a patient’s status being unexposed for the duration of the follow-up where they had not initiated the particular medication, and becoming exposed after they had first initiated the medication (past ever vs never exposure at each time point during the follow-up). All medications were modeled in this manner and both multivariable analysis, where all the medications were included simultaneously in the model, and univariable analysis, where only one medication was included at a time, were performed. Further, both analyses were adjusted for the person’s age group (66-69 years, 70-74 years, 75-79 years, 80-84 years & 85-89 years), rurality index, year person entered the study and their comorbidity score, with the last three being modeled as continuous variables with log-linear effects. Further, all the covariates used for adjustment were selected a priori and were treated as time-independent variables using the values at the onset of the study. It was important to perform multivariable analysis since many people were taking several cardiovascular medications simultaneously during the study period.

In addition to the past ever vs never exposure, we were also interested in estimating the effect of cumulative time on the medication on the prostate cancer incidence. Again, we modeled this as a time-dependent variable with time split into 6 month intervals to see the effect of the six-month incremental increase in exposure. The same analysis with the same model as used before, was performed, except that the exposure status for all the medications were replaced by the cumulative time exposed to the medications.

All statistical analysis was performed using the R software and the ‘survival’ package. Sample code used for performing the analysis can be found in the appendix section.