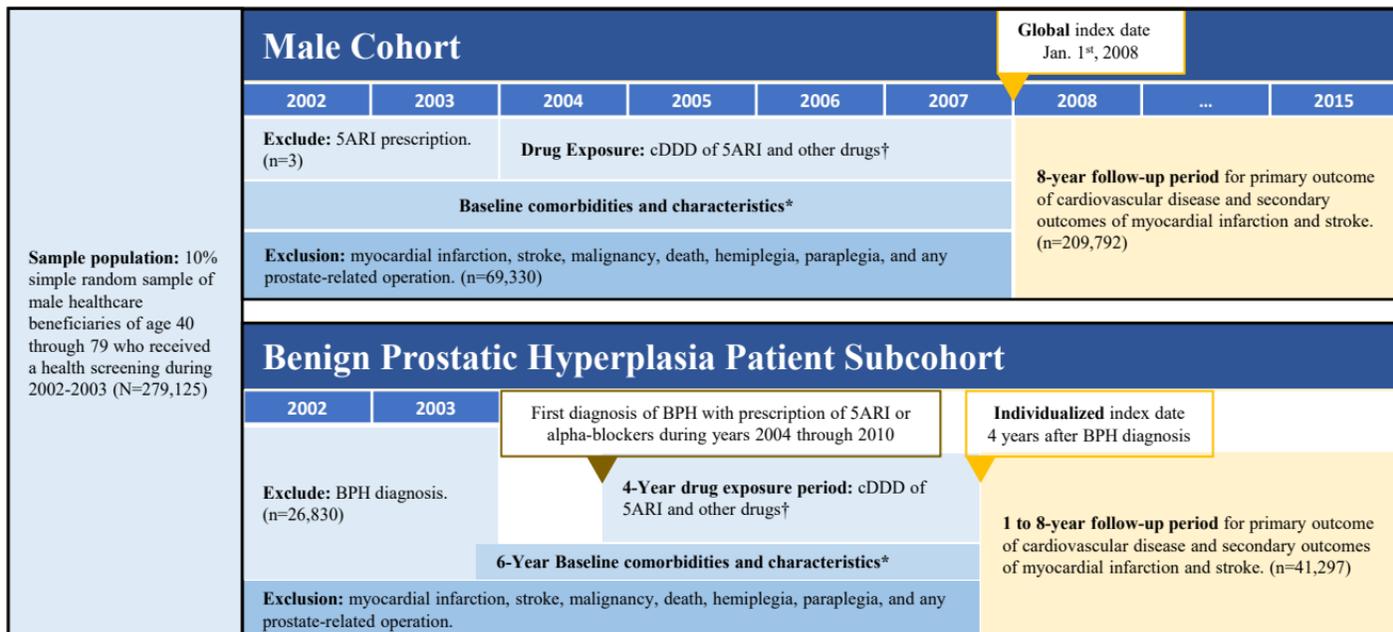


SUPPLEMENTAL MATERIAL.

Supplementary Table 1. Summary of definitions of outcomes, exclusion criteria, and comorbidities.

| Variable Type | Name of variable | Definition (ICD-10 codes plus other requirements) | |
|----------------------|--|---|---|
| Event Outcomes | Primary Outcome | Cardiovascular Disease Admission for I21-I24, I60-I69 for two or more days OR death due to I21-I24, I60-I69 | |
| | Secondary Outcomes | Myocardial Infarction | Admission for I21-I24 for two or more days OR Death due to I21-I24 |
| | | Total Stroke | Admission for I60-I69 for two or more days OR Death due to I60-I69 |
| | | Ischemic Stroke | Admission for I63 for two or more days OR Death due to I63 |
| | | Hemorrhagic Stroke | Admission for I60-I62 for two or more days OR Death due to I60-I62 |
| Exclusion Criteria | Cardiovascular Disease | I21-I24, I60-I69 | |
| | Malignancy | C00-C97 | |
| | Hemiplegia, Paraplegia | G81, G820, G821, G822 | |
| | Prostate Operation | Insurance claims procedure codes | |
| Comorbidities | Charlson Comorbidity Index | ICD-10 codes for congestive heart failure, peripheral vascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, renal disease, severe liver disease, and HIV. | |
| | Hypertension | Blood pressure greater than SBP 140 mmHg or DBP 90 mmHg measured at the latest health screening before the index date. | |
| | Diabetes | E10, E11, E12, E13, E14 plus any prescription of drugs used for treatment of diabetes, or 126 mg/dL or higher fasting blood glucose measured at the latest health screening before the index date. | |
| | High cholesterol | 240 mg/dL or higher total cholesterol measured at the latest health screening before the index date. | |
| | Acute urinary retention | R33 | |
| | BPH | N40 | |
| | Atrial Fibrillation/Flutter | I48 | |
| | Angina or chronic ischemic heart disease | I20, I251, I258, I259 | |

Supplementary Figure 1. Diagram of the male cohort and benign prostatic hyperplasia subcohort study designs



Abbreviations: 5ARI, 5-alpha reductase inhibitor; cDDD, cumulative daily defined dose; BPH, benign prostatic hyperplasia.

† Alpha-blocker, HMG-CoA reductase inhibitor, metformin, aspirin, and non-aspirin NSAID.

* Age, body mass index, smoking habit, alcohol consumption frequency, exercise frequency, quartiles of socioeconomic status, number of outpatient visits, angina, hypertension, diabetes, high cholesterol, acute urinary retention, benign prostatic hyperplasia, atrial fibrillation/flutter, Charlson Comorbidity Index (including congestive heart failure, peripheral vascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, renal disease, severe liver disease, and HIV).

Supplementary Table 2. Hazard ratios of 5ARI users vs. non-users after stratification by cardiovascular risk factors

| | | CVD (Stroke or MI) | Myocardial Infarction | Stroke |
|--------------------|------------------------------|---------------------------|---------------------------|---------------------------|
| | | aHR [†] (95% CI) | aHR [†] (95% CI) | aHR [†] (95% CI) |
| <i>Main cohort</i> | Age | | | |
| | <60 years | 0.89 (0.64-1.23) | 1.08 (0.60-1.97) | 0.81 (0.55-1.20) |
| | ≥60 years | 1.13 (0.95-1.33) | 1.14 (0.78-1.66) | 1.12 (0.93-1.35) |
| | Hypertension | | | |
| | No | 1.08 (0.89-1.31) | 1.22 (0.82-1.83) | 1.04 (0.83-1.30) |
| | Yes | 1.03 (0.82-1.29) | 0.91 (0.53-1.55) | 1.06 (0.83-1.36) |
| | Diabetes | | | |
| | No | 1.02 (0.86-1.21) | 1.17 (0.82-1.69) | 0.99 (0.81-1.20) |
| | Yes | 1.19 (0.89-1.61) | 1.01 (0.50-2.04) | 1.24 (0.89-1.72) |
| | <i>BPH Patient Subcohort</i> | Age | | |
| <60 years | | 1.03 (0.87-1.21) | 0.93 (0.68-1.28) | 1.06 (0.88-1.28) |
| ≥60 years | | 0.94 (0.86-1.03) | 0.85 (0.68-1.05) | 0.96 (0.87-1.05) |
| Hypertension | | | | |
| No | | 0.96 (0.87-1.05) | 0.94 (0.76-1.15) | 0.96 (0.87-1.07) |
| Yes | | 0.92 (0.81-1.06) | 0.67 (0.48-0.95) | 0.98 (0.84-1.13) |
| Diabetes | | | | |
| No | | 0.94 (0.86-1.02) | 0.87 (0.72-1.06) | 0.95 (0.87-1.05) |
| Yes | 0.99 (0.83-1.18) | 0.79 (0.53-1.18) | 1.04 (0.85-1.27) | |

Abbreviations: 5ARI, 5-alpha reductase inhibitor; CVD, cardiovascular disease; MI, myocardial infarction; aHR, adjusted hazard ratio; ref., referent.

[†] Using a multivariate cox proportional hazard (Wald χ^2 test P -value<0.001) adjusted for age, hypertension, diabetes, high cholesterol, body mass index, smoking habit, alcohol consumption frequency, exercise frequency, socioeconomic status in quartiles, benign prostatic hyperplasia, acute urinary retention, atrial fibrillation or flutter, angina, Charlson Comorbidity Index, outpatient visits, alpha-blocker use, aspirin use, NSAID use, HMG-CoA reductase inhibitor use, and year of first 5ARI prescription or year of BPH diagnosis (for BPH patient subcohort).

Supplementary Table 3. Hazard ratios of tertiles of 5ARI users vs. non-users

| | Exposure to 5ARI | | | |
|------------------------------|------------------|------------------|------------------|-------------------------|
| | Non-user | Q1 of user | Q2 of user | Q3 of user |
| <i>Main cohort</i> | | | | |
| 5ARI exposure, cDDD | 0 | 1-30 | 31-130 | ≥131 |
| CVD (Stroke or MI) | | | | |
| Cases | 10,101 | 276 | 227 | 241 |
| aHR† (95% CI) | 1(ref.) | 1.12 (0.95-1.33) | 1.05 (0.87-1.46) | 0.86 (0.71-1.07) |
| Myocardial Infarction | | | | |
| Cases | 2,387 | 62 | 38 | 48 |
| aHR† (95% CI) | 1(ref.) | 1.29 (0.90-1.86) | 0.85 (0.62-1.46) | 0.91 (0.56-1.48) |
| Stroke | | | | |
| Cases | 7,682 | 215 | 185 | 187 |
| aHR† (95% CI) | 1(ref.) | 1.08 (0.90-1.31) | 1.07 (0.87-1.31) | 0.85 (0.67-1.08) |
| <i>BPH patient subcohort</i> | | | | |
| 5ARI exposure, cDDD | 0 | 1-42 | 43-216 | ≥217 |
| CVD (Stroke or MI) | | | | |
| Cases | 1,348 | 556 | 509 | 471 |
| aHR† (95% CI) | 1(ref.) | 1.02 (0.93-1.13) | 0.97 (0.88-1.07) | 0.81 (0.70-0.92) |
| Myocardial Infarction | | | | |
| Cases | 285 | 110 | 85 | 87 |
| aHR† (95% CI) | 1(ref.) | 1.01 (0.81-1.26) | 0.83 (0.66-1.04) | 0.69 (0.50-0.95) |
| Stroke | | | | |
| Cases | 1,067 | 446 | 424 | 386 |
| aHR† (95% CI) | 1(ref.) | 1.02 (0.91-1.15) | 1.00 (0.90-1.12) | 0.84 (0.72-0.98) |

Abbreviations: 5ARI, 5-alpha reductase inhibitor; cDDD, cumulative daily defined dose; CVD, cardiovascular disease; aHR, adjusted hazard ratio; ref., referent; Q, quantile(tertile).

† Using a multivariate cox proportional hazard (Wald χ^2 test P -value<0.001) adjusted for age, hypertension, diabetes, high cholesterol, body mass index, smoking habit, alcohol consumption frequency, exercise frequency, socioeconomic status in quartiles, acute urinary retention, atrial fibrillation or flutter, angina, Charlson Comorbidity Index, outpatient visits, alpha-blocker use, aspirin use, NSAID use, and HMG-CoA reductase inhibitor use. Main cohort was additionally adjusted for benign prostatic hyperplasia and year of first 5ARI prescription; BPH patient subcohort, the year of BPH diagnosis.