CLINICAL RESEARCH STUDY

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The Cardiovascular Safety of Five-Alpha-Reductase Inhibitors Among Men with Benign Prostatic Hyperplasia: A Population-Based Cohort Study

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ABSTRACT

BACKGROUND: Five-alpha reductase inhibitors (5αRIs) are used to treat benign prostatic hyperplasia (BPH). However, the cardiovascular effects of 5αRIs remain poorly understood. The study objective was to compare the rate of hospitalization for heart failure among men with BPH prescribed 5αRIs to that of men with BPH not prescribed BPH medications.

METHODS: Using the Clinical Practice Research Datalink linked with hospitalization and vital statistics data, we conducted a population-based cohort study among patients newly diagnosed with BPH. We defined exposure as the current use of 5αRIs, current use of alpha-blockers, and no current use of BPH medications in a time-varying approach. The primary endpoint was hospitalization for heart failure, and secondary endpoints were myocardial infarction, stroke, and cardiovascular death. We used time-dependent Cox-proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS: Our cohort included 94,440 men with incident BPH. A total of 3893 hospitalizations for heart failure occurred over 527,660 person-years of follow-up (incidence rate 7.38; 95% CI, 7.15-7.61, per 1000 person-years). Compared with no current use of BPH medications, current use of 5αRIs was not associated with an increased risk of hospitalization for heart failure (HR 0.94; 95% CI, 0.86-1.03), myocardial infarction (HR 0.92; 95% CI, 0.81-1.05), stroke (HR 0.94; 95% CI, 0.85-1.05), or cardiovascular death (HR 0.89; 95% CI, 0.80-0.99).

CONCLUSIONS: The use of 5αRIs was not associated with an increased risk of hospitalization for heart failure, myocardial infarction, stroke, or cardiovascular death compared with non-use.

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KEYWORDS: Alpha-blockers; Benign prostatic hyperplasia; Cardiovascular safety; Cohort study; Five-alpha reductase inhibitors; heart failure

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Conflict of Interest: HTA is an employee of Merck. Finasteride, which is one of the 5-alpha reductase inhibitors and is sold under the brand name Proscar®, is manufactured by Merck. However, HTA conducted this study during his postdoctoral fellowship at McGill University prior to his employment at Merck. RWP reports personal fees from Biogen, Boehringer Ingelheim, Merck, Pfizer, and Analysis Group, outside the submitted work. LA reports consulting fees from Janssen and Pfizer for work unrelated to this study. The remaining authors have no relationships to disclose.

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BACKGROUND

Benign prostatic hyperplasia (BPH) is a common condition that blocks the flow of urine out of the bladder and can cause uncomfortable urinary symptoms as men age.[1] Symptoms are managed by lifestyle modification, use of medications including 5-alpha reductase inhibitors (5αRIs) and α-adrenergic antagonists (commonly referred to as "α-blockers"), or surgery.[2] Alpha-blockers are used as first-line treatment for patients with moderate-to-severe lower urinary tract symptoms.[3] Five-alpha reductase inhibitors are recommended for patients with enlarged prostate, increased prostate specific antigen (PSA), or both, and moderate-to-severe lower urinary tract symptoms.[3] The use of 5αRIs and α-blockers has substantially increased over the past 2 decades.[4]

There is a biological rationale that supports a potential increased risk of cardiovascular events associated with the use of 5αRIs. 5αRIs inhibit the 5α-reductase enzyme, resulting in lower levels of the active testosterone metabolite dihydrotestosterone.[5] A large body of evidence exists linking decreased dihydrotestosterone levels with adverse cardiovascular effects.[6,7] The REDUCE prostate cancer prevention trial revealed an increased risk of a composite endpoint of cardiac failure among patients randomized to dutasteride compared with those randomized to placebo.[8] However, this study was not adequately powered to detect the risk of cardiac failure of 5αRIs. The subsequent systematic review showed no association between the use of dutasteride and the risk of heart failure.[9] However, this review had several important limitations, including the inclusion of sub-therapeutic dutasteride dosages (range: 0.01 to 5 mg), the exclusion of studies on finasteride (another most commonly prescribed 5αRI), and the analysis of a relatively healthy population that may not be generalizable. A case control study nested within a cohort of 4414 men (aged ≥30 years) who had a history BPH medication use between 1992 and 1998 examined the cardiovascular safety of 5αRIs.[10] This study reported that there were no statistically significant association between the use of finasteride and hospitalization of ischemic heart diseases. However, this case control study suffered from several methodological limitations. We therefore conducted a retrospective cohort study to evaluate the association between 5αRI use and risk of hospitalization for heart failure among men with newly diagnosed with BPH.

CLINICAL SIGNIFICANCE

- Despite a biological rationale supporting adverse cardiovascular effect of 5-alpha reductase inhibitors, only a small number of previous studies, with important methodological limitations, have assessed this risk.
- The association between 5-alpha reductase inhibitors and the risk of hospitalization for heart failure in men with benign prostatic hyperplasia was examined using time-dependent Cox-proportional hazard models.
- Compared with non-use of benign prostatic hyperplasia medications, 5-alpha reductase inhibitors use was not associated with an increased risk of hospitalization for heart failure.

METHODS

Data Source

We used the United Kingdom's Clinical Practice Research Datalink (CPRD) Gold. Clinical Practice Research Datalink data were linked to Hospital Episode Statistics (HES) data, which contains detailed hospitalization data, and to Office for National Statistics (ONS) vital statistics data, which contain causes of death. The CPRD is a clinical database that contains electronic records for over 11 million patients from over 700 general practitioner practices.[11] It is broadly considered representative of the UK population with respect to age, sex, and ethnicity and covers approximately 11% of the UK population. CPRD data include demographic data, lifestyle information, clinical diagnoses, preventive care and immunizations, laboratory tests, and specialist referrals and consultations. CPRD uses Read codes to record clinical diagnoses, a hierarchical clinical classification system that contains over 96,000 codes.[11] It uses British National Formulary coding and product codes to capture all prescriptions generated by the general practitioner. In the HES, diagnoses are recorded using the International Classification of Diseases (ICD) 10th revision coding system.[11] ONS records causes of death using ICD-9th (pre-2001) and ICD-10th (2001 onward) codes. CPRD data have been previously validated and are of high quality.[11,12]

This study underwent scientific and ethical review by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (ISAC number 16_265A2) and ethical review by the Research Ethics Board of the Jewish General Hospital in Montreal, Canada (17-008). Herein, we followed the latest Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines (Supplementary Table 1, available online).

Study Population

Our cohort included men aged ≥40 years with a recorded diagnosis of BPH in the CPRD between January 1, 1998, and March 31, 2016. The date of their first recorded BPH diagnosis defined the cohort entry date (Supplementary Table 2, available online). The study was restricted to those with at least 1 year of CPRD history before cohort entry to ensure sufficient observation time to assess comorbidities and other potential confounders. We excluded those with a Read code for BPH before the study period to restrict the study to those

with incident BPH. We also excluded patients who received prescriptions for the BPH of interest in the year before cohort entry to avoid biases associated with the study of prevalent users.[13] We further excluded patients with a diagnosis of prostate cancer prior to cohort entry, as 5αRIs may be used off-label in these patients and cancer and its treatments are associated with an increased risk of cardiovascular disease.[14,15] Because this study aimed to be representative of real-life practice, we did not exclude patients with heart failure or other cardiovascular diseases at cohort entry. In the primary analysis, patients were followed from cohort entry until the occurrence of a study endpoint (defined below) or censoring due to all-cause mortality, a diagnosis of prostate cancer, departure from the CPRD, or the end of the study period (March 31, 2016), whichever occurred first. Non-cardiovascular death was censored when the risk of the cardiovascular death was assessed.

Exposure

Exposure was assessed in a time-dependent fashion such that each patient's exposure status was updated daily during follow-up. We classified patients using the following 3 mutually exclusive exposure categories: 1) currently exposed to 5αRIs (with or without α-blockers); 2) currently exposed to α-blockers only; 3) currently unexposed to either drug class (i.e., previous users of 5αRIs or α-blockers and those whose BPH was not treated with medication). We classified patients as currently exposed to a study drug at follow-up time *t* if the duration of the prescription + a 30-day grace period (to account for non-adherence and the biological half-life of the medication) overlapped with time *t*. In secondary analyses, we examined the current use of dutasteride and finasteride as separate exposure categories. In situations where patients switched between medications, we considered them exposed to the newly prescribed medication immediately upon its prescription. The primary comparison group was men who were not currently taking 5αRIs or α-blockers. We selected non-use as our primary reference category rather than α-blockers as this class of medications has known anti-hypertensive effects. In a secondary analysis, we used α-blockers as an active comparator to examine the comparative cardiovascular safety of 5αRIs.

Outcome

The primary endpoint was hospitalization for heart failure, defined by an ICD-9 or ICD-10 code (Supplementary Table 3, available online) indicating a recorded diagnosis of heart failure in HES or heart failure as an underlying cause of death in ONS. Secondary endpoints included myocardial infarction, stroke, and death from cardiovascular causes. These secondary endpoints were defined independently of each other, with separate follow-up durations calculated for each endpoint. Myocardial infarction and stroke were defined using HES (ICD-10 codes) and ONS (ICD-9 or ICD-10 codes). The date of admission defined the cardiovascular events date. In the secondary analyses, death with cardiovascular diseases as the primary causes of death was defined using ONS. The date of death defined the cardiovascular death event date.

Potential Confounders

We have adjusted for demographic, socioeconomic, cardio adverse and cardioprotective comorbidities, and medications. The detail of confounder assessment can be found in the Supplementary Method 1, available online.

Statistical Analysis

We presented descriptive statistics of our cohort at the time of cohort entry as counts and proportions (categorical variables) or means and standard deviations (continuous variables). Incidence rates with 95% confidence intervals (CIs) were estimated using Poisson regression overall and by exposure group. For our primary analysis, we used a time-dependent Cox proportional hazards model to estimate the adjusted hazard ratio (HR) and 95% CI for hospitalization for heart failure for current use of 5αRIs vs non-use of BPH medications. Missing data for smoking, body mass index, and Index of Multiple Deprivation were imputed with 5 multiple imputations and the estimates were pooled using Rubin's rule.[16,17] The proportional hazard assumption was met for the crude and adjusted models (Supplementary Figure, available online).

In secondary analyses, we repeated our analyses for each of the following endpoints: myocardial infarction, stroke, and death from cardiovascular causes. In addition, we estimated HRs for the primary and secondary endpoints with current use of α-blockers as the reference category. Finally, to compare the risk of cardiovascular events among men with BPH prescribed dutasteride to that in men with BPH prescribed finasteride, we subclassified 5αRIs by molecule.

To assess the robustness of our results, we conducted 9 sensitivity analyses (Supplementary Method 2, available online).

RESULTS

Study Cohort

Among the 231,174 men with a diagnosis of BPH in the CPRD, 116,597 had incident BPH between January 1, 1998, and March 31, 2016 (Figure 1). After the application of the inclusion and exclusion criteria, 94,440 patients were included in the study cohort (4114 exposed to 5αRIs, 23,551 exposed to α-blockers, and 66,775 not exposed to 5αRIs or α-blockers at baseline). With a median follow-up time of 4.7 years (interquartile-range [IQR]: 2.0 to 8.5 years), our cohort for the primary analysis generated 527,660 person-years of follow-up.

Patient Characteristics

Table 1 presents the baseline demographic and clinical characteristics of our study population. Overall, the mean

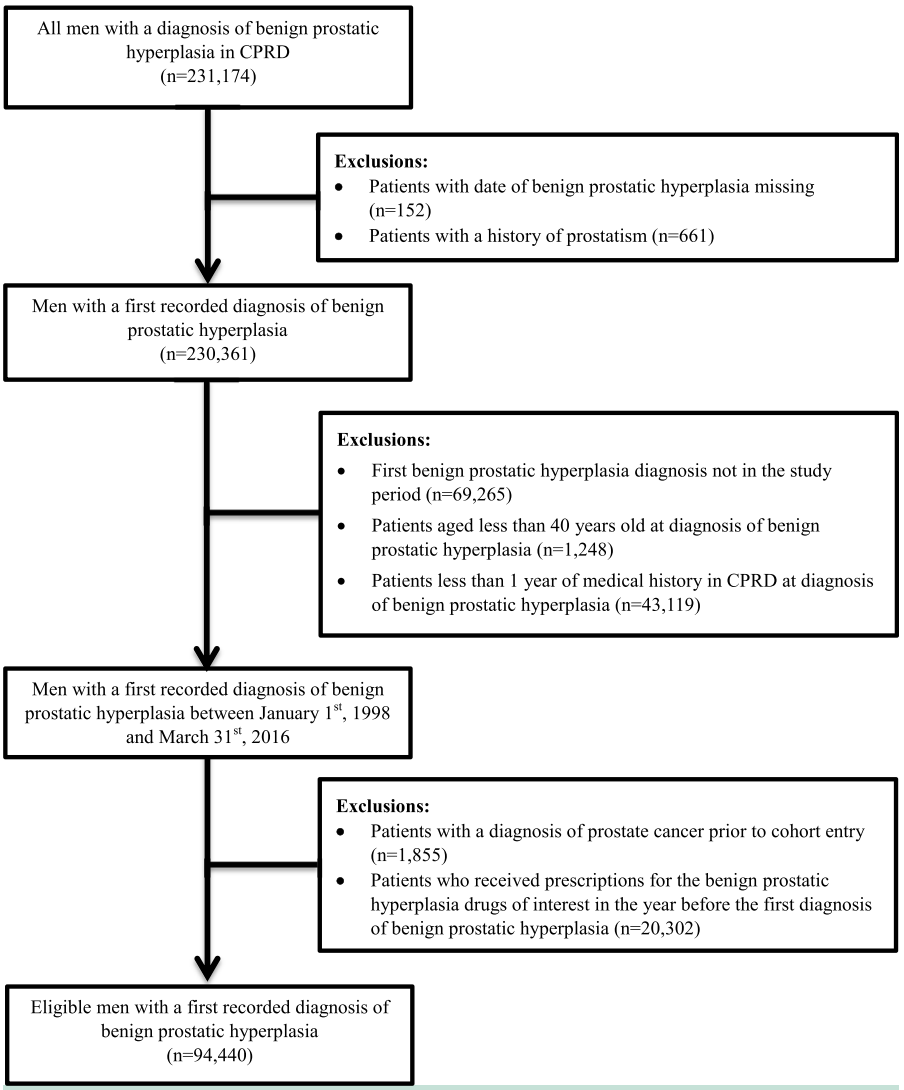

Figure 1 Flow diagram describing construction of cohort of men with incident BPH in the UK CPRD from 1998-2016. BPH = benign prostatic hyperplasia; CPRD = Clinical Practice Research Datalink.

age was 66.2 years. Patients in the 5αRIs group tended to be older than patients taking α-blockers and patients with no prescription for BPH at baseline. At baseline, 16.8% of study participants were in the least deprived category, and 53% were ever smokers. Overall, 16.6% had type 2 diabetes, 37% had hypertension, and 28.3% had used statin. There were also some notable differences in terms of comorbidities at baseline. For example, patients with 5αRIs had a greater prevalence of comorbidities than patients with no treatment at baseline, including coronary artery disease, chronic obstructive pulmonary disease, hypertension, previous myocardial infarction, and previous stroke. Additional data on regions and calendar year at cohort entry and total population are listed in Supplementary Tables 4 and 5 (available online).

Cardiovascular Outcomes

During the time of 5αRIs use, α-blocker use, and nonuse, a total of 580, 1067, and 2246 incident episodes of hospitalization for heart failure occurred representing incidence rates of 10.4 (95% CI, 9.6-11.3), 8.5 (95% CI, 8.0-9.0), and 6.5 (95% CI, 6.2-6.8) per 1000 person-years, respectively. The use of 5αRIs was not associated with an increased risk of hospitalization for heart failure compared with no current use of BPH drugs (HR 0.94; 95% C, 0.86-1.03). Similarly, the use of 5αRIs was not associated with increased risks of myocardial infarction, stroke, and cardiovascular death compared with no current use of BPH drugs (Table 2 and Figure 2).

Table 1 Baseline Characteristics of Patients with Benign Prostatic Hyperplasia Diagnosis in the United Kingdom Between 1998 And 2016

Baseline Characteristics	5αRIs (n = 4114), 4.36%	α-blockers Only (n = 23,551), 24.94%	No Use (n = 66,775), 70.71%
Age, mean (SD)	69.9 (10.0)	67.3 (10.2)	65.6 (10.4)
<55 years (%)	296 (7.2)	2913 (12.4)	10,704 (16.0)
55-64 years (%)	1036 (25.2)	7005 (29.7)	21,939 (32.9)
65-74 years (%)	1441 (35.0)	8018 (34.0)	20,985 (31.4)
75-84 years (%)	1085 (26.4)	4682 (19.9)	11,145 (16.7)
≥85 years (%)	256 (6.2)	933 (4.0)	2002 (3.0)
Index of Multiple Deprivation			
1 (least deprived) (%)	558 (13.6)	3551 (15.1)	11,713 (17.5)
2 (%)	604 (14.7)	3491 (14.8)	11,367 (17.0)
3 (%)	478 (11.6)	2795 (11.9)	8552 (12.8)
4 (%)	445 (10.8)	2483 (10.5)	6822 (10.2)
5 (%)	288 (7.0)	1657 (7.0)	3713 (5.6)
Unknown (%)	1741 (42.3)	9574 (40.7)	24,608 (36.9)
BMI			
≥30 kg/m^2 (%)	708 (17.2)	4446 (18.9)	9997 (15.0)
<30 kg/m^2 (%)	2334 (56.7)	12,657 (53.7)	33,923 (50.8)
Unknown (%)	1072 (26.1)	6448 (27.4)	22,885 (34.2)
Alcohol use, yes (%)	191 (4.6)	1121 (4.8)	2507 (3.8)
Smoking			
Ever smoker (%)	2383 (57.9)	13,489 (57.3)	34,172 (51.2)
Never smoker (%)	1183 (28.8)	6442 (27.3)	17,506 (26.2)
Unknown (%)	548 (13.3)	3620 (15.4)	15,097 (22.6)
PSA testing in the previous year			
0-4 ng/ml, n (%)	1387 (33.7)	8599 (36.5)	11,893 (17.8)
4-10 ng/ml, n (%)	473 (11.5)	1821 (7.7)	5241 (7.8)
10-20 ng/ml, n (%)	126 (3.1)	347 (1.5)	1514 (2.3)
20+ ng/ml, n (%)	46 (1.1)	158 (0.7)	929 (1.4)
Unknown, n (%)	2082 (50.6)	12,626 (53.6)	47,198 (70.7)
General practitioner visits, mean (SD)	1.5 (0.7)	1.5 (0.6)	1.4 (0.6)
0, n (%)	2262 (55.0)	13,712 (58.2)	42,024 (62.9)
1-6, n (%)	1616 (39.3)	8787 (37.3)	22,427 (33.6)
7-12, n (%)	178 (4.3)	773 (3.3)	1711 (2.6)
13-24, n (%)	48 (1.2)	238 (1.0)	514 (0.8)
≥25, n (%)	10 (0.2)	41 (0.2)	99 (0.1)
Number of hospitalizations, mean (SD)	0.2 (0.6)	0.1 (0.5)	0.1 (0.5)
0 (%)	3679 (89.4)	21,696 (92.1)	62,184 (93.1)
1 (%)	288 (7.0)	1322 (5.6)	3343 (5.0)
>1 (%)	147 (3.6)	533 (2.3)	1248 (1.9)
Number of drug classes, mean (SD)	8.7 (5.8)	7.8 (.5.5)	5.6 (5.0)
Surgical intervention for BPH, n (%)	354 (8.6)	936 (4.0)	2842 (4.3)
Charlson Comorbidity Index			
Mean (SD)	1.3 (1.7)	1.2 (1.6)	0.9 (1.4)
0, n (%)	1782 (43.3)	11,216 (47.6)	36,600 (54.8)
1, n (%)	969 (23.6)	5590 (23.7)	15,476 (23.2)
2+, n (%)	1363 (33.1)	6745 (28.6)	14,699 (22.0)
Coronary artery disease, n (%)	1001 (24.3)	4619 (19.6)	11,697 (17.5)
Cerebrovascular disease, n (%)	446 (10.8)	2042 (8.7)	4537 (6.8)
Chronic obstructive pulmonary disease, n (%)	599 (14.6)	2981 (12.7)	7421 (11.1)
Type 2 diabetes, n (%)	861 (20.9)	4829 (20.5)	10,034 (15.0)
Hypertension, n (%)	1838 (44.7)	9875 (41.9)	23,508 (35.2)
Dyslipidemia, n (%)	1062 (25.8)	5742 (24.4)	13,437 (20.1)
Depression, n (%)	713 (17.3)	4608 (19.6)	11,379 (17.0)
Peripheral vascular disease, n (%)	220 (5.3)	1102 (4.7)	2608 (3.9)

Table 1 (*Continued*)

Baseline Characteristics	5αRIs (n = 4114), 4.36%	α-blockers Only (n = 23,551), 24.94%	No Use (n = 66,775), 70.71%
Previous coronary revascularization, n (%)	315 (7.7)	1558 (6.6)	3701 (5.5)
Previous myocardial infarction, n (%)	432 (10.5)	1889 (8.0)	4860 (7.3)
Previous stroke, n (%)	397 (9.6)	1816 (7.7)	4047 (6.1)
Sleep apnea, n (%)	48 (1.2)	357 (1.5)	758 (1.1)
Cancers other than prostate cancer, n (%)	396 (9.6)	1839 (7.8)	4072 (6.1)
Acetylsalicylic acid, n (%)	1318 (32.0)	6309 (26.8)	14,608 (21.9)
Angiotensin-converting enzyme inhibitors, n (%)	1050 (25.5)	5264 (22.3)	12,445 (18.6)
Angiotensin receptor blockers, n (%)	362 (8.8)	1782 (7.6)	3553 (5.3)
Antidepressants, n (%)	312 (7.6)	2073 (8.8)	4476 (6.7)
β-blockers, n (%)	870 (21.1)	4239 (18.0)	10,749 (16.1)
Calcium-channel blockers, n (%)	898 (21.8)	4900 (20.8)	10,981 (16.4)
Diuretics, n (%)	985 (23.9)	4333 (18.4)	11,298 (16.9)
Fibrates, n (%)	39 (0.9)	205 (0.9)	558 (0.8)
Smoking cessation drugs, n (%)	57 (1.4)	393 (1.7)	948 (1.4)
Non-steroidal anti-inflammatory drugs, n (%)	900 (21.9)	5428 (23.0)	14,103 (21.1)
Statins, n (%)	1521 (37.0)	7966 (33.8)	17,269 (25.9)

5αRIs = 5-alpha reductase inhibitors; α-blockers = alpha-blockers; β-blockers = beta-blockers; BMI = Body mass index; BPH = benign prostatic hyperplasia; CI = confidence interval; PYs = person-years, PSA = prostate-specific antigen; SD = standard deviation.

Secondary Analyses

The results of our secondary analyses are reported in Tables 3 and 4. We did not observe a statisticaly signficant association between the risk of hospitalization for heart failure, myocardial infarction, or stroke when current use of 5αRIs was compared with current use of α-blockers (Table 3). However, 5αRIs were associated with an increased risk of cardiovascular death compared with α-blockers (HR 1.18; 95% CI, 1.04-1.33). Molecule-specific analyses did not reveal an increased risk of

Table 2 The Crude and Adjusted Hazard Ratios and 95% Confidence Intervals for Cardiovascular Events Associated with 5αRIs Among Men with Benign Prostatic Hyperplasia Diagnosis in the United Kingdom Between 1998 and 2016*

Exposure	No of Events	PYs	Incidence Rate 95% CI (per 1000 PYs)	Crude HR (95% CI)	Adjusted HR† (95% CI)
Heart failure					
Currently not exposed	2246	346,192	6.5 (6.2-6.8)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	1067	125,577	8.5 (8.0-9.0)	1.30 (1.21-1.40)	1.00 (0.93-1.07)
Currently exposed to 5αRIs	580	55,891	10.4 (9.6-11.3)	1.58 (1.44-1.73)	0.94 (0.86-1.03)
Myocardial infarction					
Currently not exposed	1476	347,060	4.3 (4.0-4.5)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	587	126,131	4.7 (4.3-5.1)	1.09 (0.99-1.20)	0.92 (0.84-1.02)
Currently exposed to 5αRIs	295	56,352	5.0 (4.8-5.9)	1.21 (1.07-1.38)	0.92 (0.81-1.05)
Stroke					
Currently not exposed	1774	346,909	5.1 (4.9-5.4)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	697	125,951	5.5 (5.1-6.0)	1.08 (0.99-1.18)	0.88 (0.81-0.96)
Currently exposed to 5αRIs	418	56,226	7.4 (6.8-8.2)	1.43 (1.29-1.60)	0.94 (0.85-1.05)
Cardiovascular death					
Currently not exposed	1837	350,781	5.2 (5.0-5.5)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	622	127,461	4.9 (4.5-5.3)	0.93 (0.85-1.02)	0.75 (0.69-0.83)
Currently exposed to 5αRIs	430	57,217	7.5 (6.8-8.3)	1.40 (1.26-1.56)	0.89 (0.80-0.99)

5αRIs = 5-alpha reductase inhibitors, α-blockers = alpha-blockers; CI = confidence interval; HR = hazard ratio, IMD = Index of Multiple Deprivation, PYs = person-years.

*Missing data regarding IMD, body mass index, and smoking were imputed using multiple imputation.

†Adjusted for age, calendar year, region, IMD, lifestyle variables (body mass index, alcohol, and smoking), number of general practitioner visits, number of hospitalizations, number of drug classes, surgical interventions for BPH, Charlson comorbidity index, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, type 2 diabetes, hypertension, dyslipidemia, depression, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction, previous stroke, sleep apnea, cancers other than prostate cancer, acetylsalicylic acid, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antidepressants, beta-blockers, calcium-channel blockers, diuretics, fibrates, smoking cessation drugs, non-steroidal anti-inflammatory drugs, and statins.

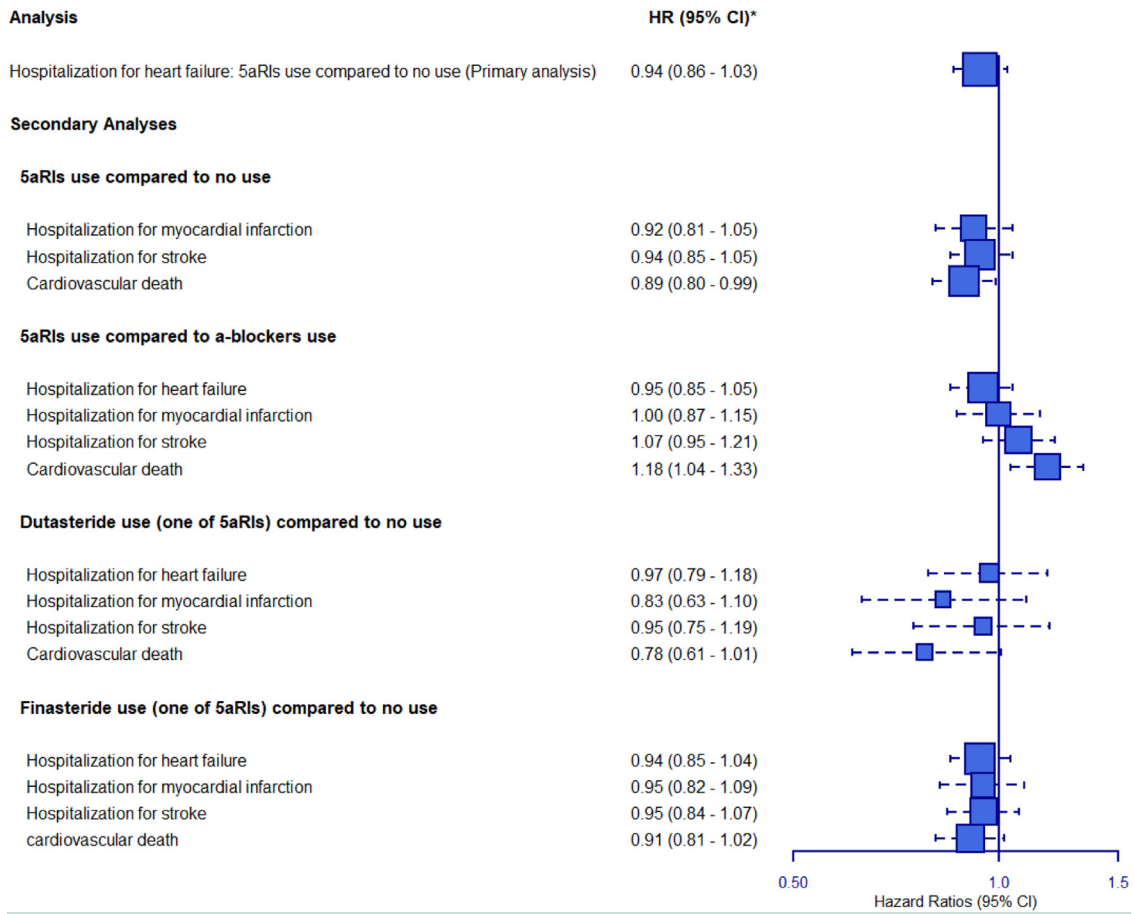

Figure 2 Forest plot showing the primary and secondary analyses for risk of cardiovascular outcomes among men with BPH with current use of 5αRIs compared with no current use of BPH medications. The follow-up was censored if dutasteride and finasteride were prescribed on the same date. 5αRIs = 5-alpha reductase inhibitors; α-blockers = alpha blockers; BPH = benign prostatic hyperplasia; CI = confidence interval; HR = hazard ratio. *Adjusted for age, calendar year, lifestyle variables (body mass index, alcohol, and smoking), number of general practitioner visits, number of hospitalizations, number of prescriptions, surgical interventions for BPH, Charlson Comorbidity Index, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, hypertension, dyslipidemia, depression, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction, previous stroke, sleep apnea, cancers other than prostate cancer, acetylsalicylic acid, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antidepressants, beta-blockers, calcium-channel blockers, diuretics, fibrates, smoking cessation drugs, non-steroidal anti-inflammatory drugs, and statins.

hospitalization for heart failure, myocardial infarction, stroke, or cardiovascular death when finasteride and dutasteride were compared with no current use of BPH drugs (Table 4). Finally, head-to-head comparisons between dutasteride and finasteride revealed no association with the risk of hospitalization for heart failure (HR 1.03; 95% CI, 0.83-1.28), myocardial infarction (HR 0.88; 95% CI, 0.65-1.19), hospitalization for stroke (HR 1.00; 95% CI, 0.78-1.28), or cardiovascular death (HR 0.86; 95% CI, 0.66-1.12).

Sensitivity Analyses

The use of 5αRIs was not associated with an increased risk of hospitalization for heart failure compared with no use of BPH medication in men with history of cardiovascular diseases (HR 1.01; 95% CI, 0.90-1.14) and without history of cardiovascular diseases (HR 0.83; 95% CI, 0.71-0.97) at baseline. All other sensitivity analyses produced estimates that were similar to those of the primary analysis (Figure 3 and Supplementary Table 6, available online).

DISCUSSION

In this large population-based study, compared with the no current use of BPH medications, the current use of 5αRIs was not associated with an increased risk of hospitalization for heart failure, myocardial infarction, stroke, or cardiovascular death among men with BPH. Similar unincreased risk of hospitalization for heart failure was observed in both men with and without prior history of heart failure at baseline. The risks of these

Table 3 Association Between the Use of 5αRIs vs α-Blockers and the Risk of Cardiovascular Diseases Among Men with Benign Prostatic Hyperplasia in the United Kingdom*

Exposure	No of Events	PYs	Incidence Rate 95% CI (per 1000 PYs)	Crude HR (95% CI)	Adjusted HR† (95% CI)
Heart failure					
Currently not exposed	2246	346,192	6.5 (6.2-6.8)	0.77 (0.71-0.83)	1.00 (0.93-1.08)
Currently exposed to α-blockers	1067	125,577	8.5 (8.0-9.0)	1.00 (Reference)	1.00 (Reference)
Currently exposed to 5αRIs	580	55,891	10.4 (9.6-11.3)	1.22 (1.10-1.35)	0.95 (0.85-1.05)
Myocardial infarction					
Currently not exposed	1476	347,060	4.3 (4.0-4.5)	0.92 (0.83-1.01)	1.08 (0.98-1.19)
Currently exposed to α-blockers	587	126,131	4.7 (4.3-5.1)	1.00 (Reference)	1.00 (Reference)
Currently exposed to 5αRIs	295	56,352	5.2 (4.7-5.9)	1.11 (0.97-1.28)	1.00 (0.87-1.15)
Stroke					
Currently not exposed	1774	346,909	5.1 (4.9-5.4)	0.92 (0.85-1.01)	1.13 (1.04-1.24)
Currently exposed to α-blockers	697	125,951	5.5 (5.1-6.0)	1.00 (Reference)	1.00 (Reference)
Currently exposed to 5αRIs	418	56,226	7.4 (6.8-8.2)	1.33 (1.17-1.50)	1.07 (0.95-1.21)
Cardiovascular death					
Currently not exposed	1837	350,781	5.2 (5.0-5.5)	1.07 (0.98-1.17)	1.33 (1.21-1.46)
Currently exposed to α-blockers	622	127,461	4.9 (4.5-5.3)	1.00 (Reference)	1.00 (Reference)
Currently exposed to 5αRIs	430	57,217	7.5 (6.8-8.3)	1.50 (1.33-1.70)	1.18 (1.04-1.33)

5αRIs = 5-alpha reductase inhibitors; α-blockers = alpha-blockers; CI = confidence interval; HR = hazard ratio; IMD = Index of Multiple Deprivation; PYs = person-years.

*Missing data regarding IMD, body mass index, and smoking were imputed using multiple imputation.

†Adjusted for age, calendar year, region, IMD, lifestyle variables (body mass index, alcohol, and smoking), number of general practitioner visits, number of hospitalizations, number of drug classes, surgical interventions for BPH, Charlson comorbidity index, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, type 2 diabetes, hypertension, dyslipidemia, depression, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction, previous stroke, sleep apnea, cancers other than prostate cancer, acetylsalicylic acid, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antidepressants, beta-blockers, calcium-channel blockers, diuretics, fibrates, smoking cessation drugs, non-steroidal anti-inflammatory drugs, and statins.

Table 4 Association Between the Use of Dutasteride and Finasteride vs No Use of Benign Prostatic Hyperplasia Treatments and the Risk of Cardiovascular Diseases Among Men with Benign Prostatic Hyperplasia in the United Kingdom*

Exposure†	No of Events	PYs	Incidence Rate 95% CI (per 1000 PYs)	Crude HR (95% CI)	Adjusted‡ HR (95% CI)
Heart failure					
Currently not exposed	2246	346,158	6.5 (6.2-6.8)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	1066	125,565	8.5 (8.0-9.0)	1.30 (1.21-1.40)	1.00 (0.92-1.07)
Currently exposed to dutasteride	107	12,082	8.9 (7.3-10.7)	1.35 (1.11-1.64)	0.97 (0.79-1.18)
Currently exposed to finasteride	473	43,658	10.8 (9.9-11.8)	1.65 (1.50-1.83)	0.94 (0.85-1.04)
Myocardial infarction					
Currently not exposed	1476	16,087,644	4.3 (4.0-4.5)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	587	126,119	4.7 (4.3-5.1)	1.09 (0.99-1.20)	0.92 (0.84-1.02)
Currently exposed to dutasteride	51	12,149	4.2 (3.2-5.5)	0.97 (0.73-1.28)	0.83 (0.63-1.10)
Currently exposed to finasteride	244	44,046	5.5 (4.9-6.3)	1.29 (1.12-1.47)	0.95 (0.82-1.09)
Stroke					
Currently not exposed	1773	346,872	5.1 (4.9-5.4)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	697	125,939	5.5 (5.1-6.0)	1.08 (0.99-1.18)	0.88 (0.81-0.96)
Currently exposed to dutasteride	77	12,099	6.4 (5.1-8.0)	1.23 (0.98-1.54)	0.95 (0.75-1.19)
Currently exposed to finasteride	341	43,968	7.8 (7.0-8.6)	1.50 (1.33-1.68)	0.95 (0.84-1.07)
Cardiovascular death					
Currently not exposed	1836	350,743	5.0 (5.0-5.5)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	622	127,450	4.9 (4.5-5.3)	0.94 (0.85-1.02)	0.75 (0.69-0.83)
Currently exposed to dutasteride	66	12,324	5.4 (4.2-6.8)	1.00 (0.78-1.27)	0.78 (0.61-1.01)
Currently exposed to finasteride	364	44,734	8.1 (7.3-9.0)	1.52 (1.36-1.70)	0.91 (0.81-1.02)

5αRIs = 5-alpha reductase inhibitors; α-blockers = alpha-blockers; BPH = benign prostatic hyperplasia; CI = confidence interval; HR = hazard ratios; IMD = Index of Multiple Deprivation; PYs = person-years.

*Missing data regarding IMD, BMI, and smoking were imputed using multiple imputation.

†The follow-up was censored when dutasteride and finasteride were prescribed on the same date

‡Adjusted for age, calendar year, region, IMD, lifestyle variables (body mass index, alcohol, and smoking), number of general practitioner visits, number of hospitalizations, number of drug classes, surgical interventions for BPH, Charlson comorbidity index, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, type 2 diabetes, hypertension, dyslipidemia, depression, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction, previous stroke, sleep apnea, cancers other than prostate cancer, acetylsalicylic acid, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antidepressants, beta-blockers, calcium-channel blockers, diuretics, fibrates, smoking cessation drugs, non-steroidal anti-inflammatory drugs, and statins.

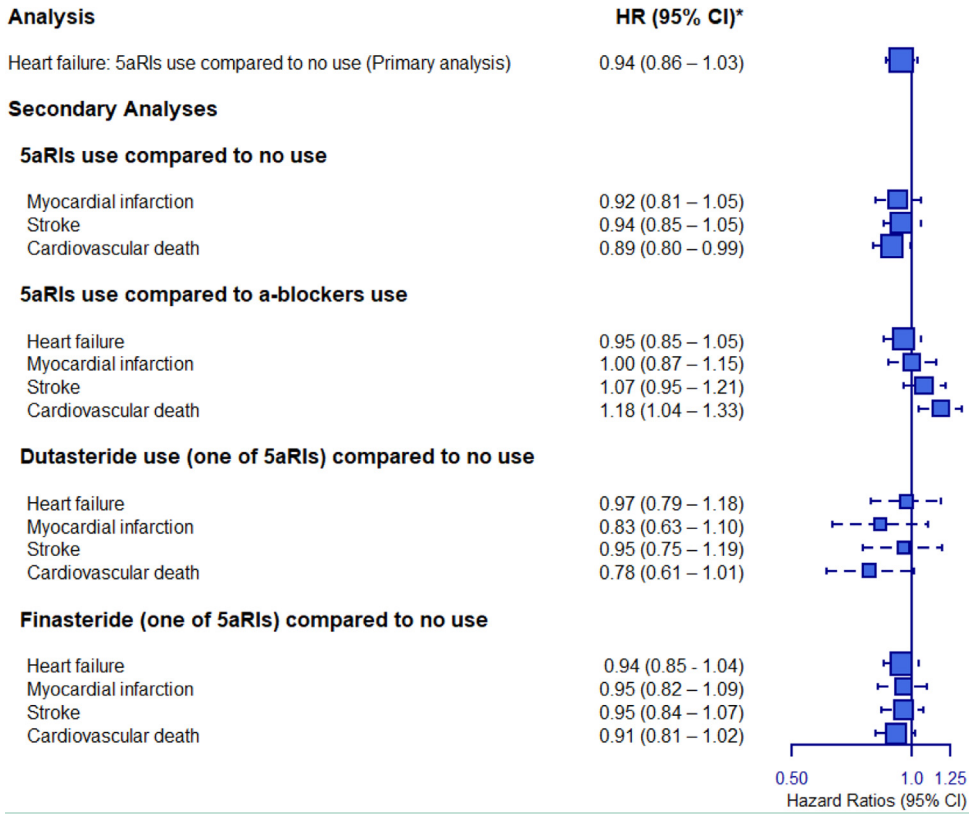

Figure 3 A forest plot showing the sensitivity analyses for risk of heart failure among patients with BPH with current use of 5αRIs compared with no use of BPH medications. 5αRIs = 5-alpha reductase inhibitors; α-blockers = alpha blockers; BPH = benign prostatic hyperplasia; CI = confidence interval; HR = hazard ratio. *Adjusted for age, calendar year, lifestyle variables (body mass index, alcohol, and smoking), number of general practitioner visits, number of hospitalizations, number of prescriptions, surgical interventions for BPH, Charlson Comorbidity Index, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, hypertension, dyslipidemia, depression, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction, previous stroke, sleep apnea, cancers other than prostate cancer, acetylsalicylic acid, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antidepressants, beta-blockers, calcium-channel blockers, diuretics, fibrates, smoking cessation drugs, non-steroidal anti-inflammatory drugs, and statins.

cardiovascular diseases were unchanged when the current use of 5αRIs were compared with the current use of α-blockers. Modest increase of the risk of cardiovascular death (HR 1.18; 95% CI, 1.04-1.33) was observed with use of 5αRIs compared with α-blockers use requiring further investigation. This could be due to the cardioprotective effect of α-blockers. No difference was observed between 5αRIs in molecule-specific analyses. Sensitivity analyses produced consistent results to that of primary analyses, suggesting that our results were robust to study assumptions.

Previous studies examined the potential mechanisms behind this potential drug safety issue.[18–20] It was hypothesized that the potential reduction of dihydrotestosterone among BPH patients using 5αRIs could increase the risk of hospitalization for heart failure. Several studies have shown an association between androgen deprivation therapy, which reduces dihydrotestosterone levels, and an increased risk of cardiovascular diseases.[21–23] However, 5αRIs are less potent than androgen deprivation therapies, and previous studies have shown that androgen deprivation therapies increase plasma hormone levels in a dose-dependent manner.[24]

With an aging global population, the prevalence of BPH is expected to grow substantially in the coming years.[4] This demographic shift, combined with the underlying cardiovascular risk for men in this age group and the increasing use of 5αRIs over time,[4] suggests that real-world evidence regarding the cardiovascular safety of 5αRIs could have substantial clinical and public health implications. Our study, therefore, provides important reassurance regarding the cardiovascular safety of 5αRIs in this high-risk population.

The cardiovascular effects of 5αRIs have been examined previously.[8,25] First, in the CombAT trial, which was a 4-year, multicenter, randomized, double-blind, parallel-group

study, the incidence of the composite outcome cardiac failure was lower among patients randomized to dutasteride (4 of 1623; 0.2%) than among those randomized to tamsulosin monotherapy (10 of 1611; 0.6%); however, there was no difference in overall cardiovascular events across treatment groups.[25] Second, the REDUCE prostate cancer prevention trial revealed an increased risk of a composite cardiac failure endpoint among patients randomized to dutasteride compared with those randomized to placebo (relative risk 1.91; 95% CI, 1.04-3.50).[8] We did not observe such increased risk of hospitalization for heart failure, myocardial infarction, stroke, or cardiovascular death. Similarly, a systematic review and meta-analyses of 12 randomized controlled trials did not find an increased risk of cardiovascular diseases with the use of dutasteride (relative risk 1.05; 95% CI, 0.71-0.57).[9] Finally, the REDUCE and ComBAT trials were not adequately powered to assess the cardiovascular safety of 5αRIs.

This study has several strengths. First, we used the United Kingdom's CPRD, one of the largest population-based longitudinal data of primary care and our study is likely generalizable to patients treated in a real-world setting.[11] Second, our use of a time-dependent Cox model accounted to switching and discontinuation, preventing immortal time bias. Third, in our secondary analysis, we directly compared the risk of hospitalization for heart failure between 5αRIs and α-blockers use. This analysis minimized confounding by indication using an active comparator and addressed a clinically relevant question, namely the comparative safety of 5αRIs.

There are some potential limitations. First, residual confounding is a potential limitation of all observational studies. To minimize its potential impact, we used rigorous statistical adjustment, and in secondary analyses, we used an active comparator. Second, misclassification of exposure can occur because the CPRD contains data on prescriptions issued rather than on dispensations. We anticipate that the proportion of patients who do not fill their prescriptions will be small since these medications are used to alleviate symptoms rather than a decrease of a biomarker level (eg, statins and low-density lipoprotein level). In addition, misclassification of exposure can occur because of poor adherence, which would result in a bias toward the null hypothesis. Third, missing data may result in bias. However, we used multiple imputation to minimize the potential consequences of missing data.[16,17]

CONCLUSION

In our large population-based cohort study, we did not observe an association between the current use of 5αRIs and the risks of hospitalization for heart failure, stroke, myocardial infarction, or cardiovascular death among men with BPH. The results of this study, therefore, provide important reassurance regarding the cardiovascular safety of 5αRIs in this patient population.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2023.06.021.

SUPPLEMENTARY METHOD 1. POTENTIAL CONFOUNDERS AT THE COHORT ENTRY ARE INCLUDED IN ADJUSTED COX-REGRESSION MODELS ASSESSING THE ASSOCIATION BETWEEN 5αRIS AND THE RISK OF HOSPITALIZATION IN MEN WITH BENIGN PROSTATIC HYPERPLASIA IN THE UNITED KINGDOM BETWEEN 1998 AND 2016

We assessed the following potential confounders at cohort entry: demographic characteristics (age, geographic region), socio-economic status (measured by the Index of Multiple Deprivation), cohort entry year, lifestyle variables, body mass index, alcohol use, smoking status, comorbidities (coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, type 2 diabetes, hypertension, dyslipidemia, depression, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction, previous stroke, sleep apnea, and Charlson Comorbidity Index), and previous prescriptions for certain medications (acetylsalicylic acid, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, anti-depressants, beta-blockers, calcium-channel blockers, diuretics, fibrates, smoking cessation drugs, non-steroidal anti-inflammatory drugs, statins). In addition, we adjusted for cancers other than prostate cancer and surgical interventions for benign prostatic hyperplasia. We also adjusted for the number of drug classes prescribed, the number of general practitioner visits, and the number of hospitalizations in the previous year, 3 proxies for overall health. Comorbidities were defined using Read Codes in the Clinical Practice Research Data Link and International Classification of Diseases 10th revision codes in the Hospital Episode Statistics data recorded any time before cohort entry, prescriptions were defined using British National Formulary codes in the year before cohort entry, and lifestyle variables were measured any time in the 5 years before cohort entry.

SUPPLEMENTARY METHOD 2. SENSITIVITY ANALYSIS

To assess the robustness of our results, we conducted 7 sensitivity analyses. First, we censored patients who underwent surgical procedures to treat benign prostatic hyperplasia because they would less likely be prescribed benign prostatic hyperplasia medications. Second, we stratified the analyses by the presence or absence of cardiovascular disease at cohort entry to illustrate the impact of excluding such patients from clinical trials of 5-alpha reductase inhibitors (5αRIs). Third, we excluded patients with a history of hypertension from our comparison of 5αRIs and α-blockers to avoid the potential inclusion of patients using α-blockers for the treatment of hypertension. Fourth, we stratified our comparison by type of α-blocker (i.e., selective vs non-selective). Fifth, we censored patients upon the prescription for 5αRIs (Propecia®) for men pattern baldness. Sixth, we varied our grace period to 0 days and 90 days. Seventh, we used a Cox proportional hazards model with time-fixed exposure modeled using an as-treated approach and covariates assessed at cohort entry.

Two post-hoc sensitivity analyses were conducted in response to reviewers' comments. First, the risk of heart failure solely defined by hospitalization and solely defined by cause of death was assessed in men with 5αRIs use in comparison to no use. Second, we assessed the risk of hospitalization for heart failure associated with combination therapy (5αRIs and α-blockers) in comparison to no use.

Supplementary Table 1 STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Supplementary Table 2 Read Codes for the Diagnosis of Benign Prostatic Hyperplasia in the CPRD Among Men with Benign Prostatic Hyperplasia in the United Kingdom Between 1998 and 2016

Medical Codes	Read Code	Read Terminologies
2627	K20..16	Prostatism
5906	1AA..00	Prostatism
929	K200.00	Prostatic hyperplasia unspecified
1068	25Q2.11	Prostate enlarged on PR
7555	K20..15	BPH - benign prostatic hypertrophy
3045	K20..00	Benign prostatic hypertrophy
7702	K20..14	Enlarged prostate - benign
16100	14E1.00	H/O: prostatism
16035	K20z.00	Prostatic hyperplasia NOS
15346	K20..11	Benign adenoma of the prostate
25711	K20..12	Benign fibroma of prostate
35676	K202.00	Prostatic hyperplasia of the medial lobe
104567	B7C2000	Adenoma of prostate
71354	K20..13	Benign myoma of prostate
64296	K201.00	Prostatic hyperplasia of the lateral lobe

CPRD = Clinical Practice Research Data Link; H/O = history of; NOS = not otherwise specified; PR =per rectal

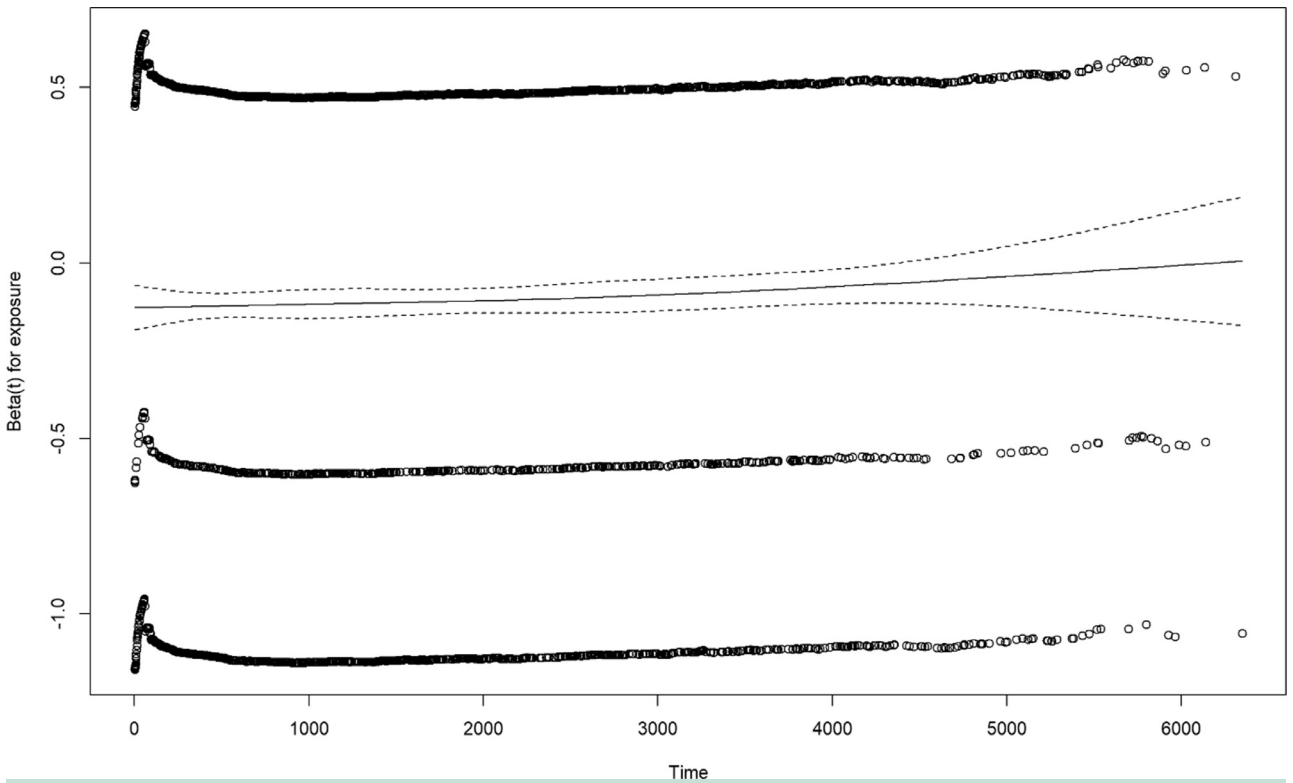
Supplementary Table 3 ICD 10 Codes in HES and IC9 Codes in ONS for the Diagnosis of Heart Failure Among Men with BPH in the United Kingdom Between 1998 and 2016

ICD 10 Codes	ICD 10 Header	ICD 9 Codes	ICD 9 Header
	Heart failure		
I11.0	Hypertensive heart disease with heart failure	428.x	Heart failure
I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease		
I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease		
I50.x	Heart failure		
	Stroke		
I63.x	Cerebral infarction	433.x	Occlusion and stenosis of precerebral arteries
I64.x	Stroke, not specified as hemorrhage or infarction	434.x	Occlusion of cerebral arteries
I67.9	Cerebrovascular disease, unspecified	435.x	Transient cerebral ischemia
G45.0	Vertebro-basilar artery syndrome	437.1	Other generalized ischemic cerebrovascular disease
G45.1	Carotid artery syndrome (hemispheric)	437.8	Other ill-defined cerebrovascular disease
G45.2	Multiple and bilateral precerebral artery syndromes	437.9	Unspecified cerebrovascular disease
G45.3	Amaurosis fugax		
G45.8	Other transient cerebral ischemic attacks and related syndromes		
G45.9	Transient cerebral ischemic attack, unspecified		
G46.x	Vascular syndromes of brain in cerebrovascular diseases		
	Myocardial infarction		
I21.X	Acute myocardial infarction	410.x	Acute myocardial infarction
	Cardiovascular death		
I00-I02	Acute rheumatic fever	390—392	Acute rheumatic fever
I05-I09	Chronic rheumatic heart diseases		
I10-I16	Hypertensive diseases	401-405	Hypertensive Disease
I20-I25	Ischemic heart diseases	410-414	Ischemic heart diseases
I26-I28	Pulmonary heart disease and diseases of pulmonary circulation	415-417	Diseases of pulmonary circulation

Supplementary Table 3 (*Continued*)

ICD 10 Codes	ICD 10 Header	ICD 9 Codes	ICD 9 Header
I30-I5A	Other forms of heart disease	420—429	Other forms of heart disease
I60-I69	Cerebrovascular diseases	430-438	Cerebrovascular Disease
I70-I79	Diseases of arteries, arterioles and capillaries	440—449	Diseases of arteries, arterioles, and capillaries
I64	Cerebral aneurysm, nonruptured	437.3	Cerebral aneurysm, nonruptured
I69.4	Sequelae of stroke, not specified as hemorrhage or infarction	438.9	Unspecified sequelae of unspecified cerebrovascular disease
I69.8	Sequelae of other and unspecified cerebrovascular diseases	I69. 998	Other sequelae following unspecified cerebrovascular disease.

ICD = International Classification of Diseases; ONS = Office of National Statistics.



Supplementary Figure The proportional hazard assumption for the model fitting the association between 5αRIs use and the risk of hospitalization for heart failure in men newly diagnosed with BPH in the United Kingdom between 1998 and 2016. The proportional hazards assumption is met when the hazard functions are proportional over time. The test of proportionality examines the interactions with time and ought to show no association with time if proportionality holds. In the crude and adjusted model, the proportional hazards assumption is met (P = .06). Moreover, the above plot is an approximation of the test for zero slope, from a least squares regression using data in the matching plot (see the survival.pdf (r-project.org)). The horizontal fitted line in the plot shows that β(t) is constant over time.

Supplementary Table 4 Baseline Characteristics of Patients' Region and Calendar Year of Enrollment for Benign Prostatic Hyperplasia Diagnosis in the United Kingdom Between 1998 and 2016

Baseline Characteristics	5αRIs (n = 4114), 4.36%	α-blockers only (n = 23,551), 24.94%	No Use (n = 66,775), 70.71%	Total (N = 94,440), 100.00%
Region				
North East, n (%)	89 (2.2)	435 (1.8)	929 (1.4)	1453 (1.5)
North West, n (%)	402 (9.8)	2782 (11.8)	6777 (10.1)	9961 (10.5)
Yorkshire and the Humber, n (%)	128 (3.1)	783 (3.3)	2816 (4.2)	3727 (3.9)
East Midlands, n (%)	106 (2.6)	660 (2.8)	3008 (4.5)	3774 (4.0)
West Midlands, n (%)	440 (10.7)	2469 (10.5)	6494 (9.7)	9403 (10.0)
East of England, n (%)	347 (8.4)	2234 (9.5)	6584 (9.9)	9165 (9.7)
South West, n (%)	438 (10.6)	1867 (7.9)	6326 (9.5)	8631 (9.1)
South Central, n (%)	431 (10.5)	2410 (10.2)	8230 (12.3)	11,071 (11.7)
London, n (%)	415 (10.1)	1970 (8.4)	6455 (9.7)	8840 (9.4)
South East Coast, n (%)	283 (6.9)	2208 (9.4)	6715 (10.1)	9206 (9.7)
Northern Ireland, n (%)	156 (3.8)	1191 (5.1)	1543 (2.3)	2890 (3.1)
Scotland, n (%)	559 (13.6)	2436 (10.3)	4697 (7.0)	7692 (8.1)
Wales, n (%)	320 (7.8)	2106 (8.9)	6201 (9.3)	8627 (9.1)
Calendar year				
1998-2001 (%)	491 (11.9)	2,788 (11.8)	13,969 (20.9)	17,248 (18.3)
2002-2005 (%)	836 (20.3)	5,229 (22.2)	18,789 (28.1)	24,854 (26.3)
2006-2009 (%)	1288 (31.3)	6,279 (26.7)	17,400 (26.1)	24,967 (26.4)
2010-2013 (%)	1131 (27.5)	6,700 (28.4)	12,452 (18.6)	20,283 (21.5)
2014-2016 (%)	368 (8.9)	2,555 (10.8)	4165 (6.2)	7088 (7.5)

5αRIs = 5-alpha reductase inhibitors; α-blockers = alpha-blockers; BPH = benign prostatic hyperplasia; n = numbers.

Supplementary Table 5 Baseline Characteristics of Patients with Benign Prostatic Hyperplasia Diagnosis in the United Kingdom Between 1998 and 2016

Baseline Characteristics	Total (N = 94,440), 100.00%
Age, mean (SD)	66.2 (10.4)
<55 years (%)	13,913 (14.7)
55-64 years (%)	29,980 (31.7)
65-74 years (%)	30,444 (32.2)
75-84 years (%)	16,912 (17.9)
≥85 years (%)	3191 (3.4)
Index of Multiple Deprivation	
1 (least deprived) (%)	15,822 (16.8)
2 (%)	15,462 (16.4)
3 (%)	11,825 (12.5)
4 (%)	9750 (10.3)
5 (%)	5658 (6.0)
Unknown (%)	35,923 (38.0)
BMI	
≥ 30 kg/m^2 (%)	15,151 (16.0)
< 30 kg/m^2 (%)	48,914 (51.8)
Unknown (%)	30,375 (32.2)
Alcohol use, yes (%)	3819 (4.0)
Smoking	
Ever smoker (%)	50,044 (53.0)
Never smoker (%)	25,131 (26.6)
Unknown (%)	19,265 (20.4)
PSA testing in the previous year	
0-4 ng/ml, n (%)	21,879 (23.2)
4-10 ng/ml, n (%)	7535 (8.0)
10-20 ng/ml, n (%)	1987 (2.1)
20+ ng/ml, n (%)	1133 (1.2)
Unknown, n (%)	61,906 (65.6)
General practitioner visits, mean (SD)	1.4 (0.6)
0, n (%)	57,998 (61.4)
1-6, n (%)	32,830 (34.8)
7-12, n (%)	2662 (2.8)
13-24, n (%)	800 (0.8)
≥25, n (%)	150 (0.2)
Number of hospitalizations, mean (SD)	0.1 (0.5)
0 (%)	87,559 (92.7)
1 (%)	4953 (5.2)
>1 (%)	1928 (2.0)
Number of drug classes, mean (SD)	6.3 (5.3)
Surgical intervention for BPH, n (%)	4132 (4.4)
Charlson Comorbidity Index	
Mean (SD)	1.0 (1.4)
0, n (%)	49,598 (52.5)
1, n (%)	22,035 (23.3)
2+, n (%)	22,807 (24.1)
Coronary artery disease, n (%)	17,317 (18.3)
Cerebrovascular disease, n (%)	7025 (7.4)
Chronic obstructive pulmonary disease, n (%)	11,001 (11.6)
Type 2 diabetes, n (%)	15,724 (16.6)
Hypertension, n (%)	35,221 (37.3)
Dyslipidemia, n (%)	20,241 (21.4)
Depression, n (%)	16,700 (17.7)
Peripheral vascular disease, n (%)	3930 (4.2)
Previous coronary revascularization, n (%)	5574 (5.9)
Previous myocardial infarction, n (%)	7181 (7.6)
Previous stroke, n (%)	6260 (6.6)
Sleep apnea, n (%)	1163 (1.2)
Cancers other than prostate cancer, n (%)	6307 (6.7)
Acetylsalicylic acid, n (%)	22,235 (23.5)
Angiotensin-converting enzyme inhibitors, n (%)	18,759 (19.9)
Angiotensin receptor blockers, n (%)	5697 (6.0)
Antidepressants, n (%)	6861 (7.3)
Beta-blockers, n (%)	15,858 (16.8)
Calcium-channel blockers, n (%)	16,779 (17.8)
Diuretics, n (%)	16,616 (17.6)
Fibrates, n (%)	802 (0.8)
Smoking cessation drugs, n (%)	1398 (1.5)
Non-steroidal anti-inflammatory drugs, n (%)	20,431 (21.6)
Statins, n (%)	26,756 (28.3)

5αRIs = 5-alpha reductase inhibitors; α-blockers = alpha-blockers, BMI = body mass index; BPH = benign prostatic hyperplasia; CI = confidence interval; PYs = person-years, PSA = prostate-specific antigen; SD = standard deviation.

Supplementary Table 6 Association Between the Use of 5αRIs vs α-Blockers and the Risk of Cardiovascular Diseases Among Men with Benign Prostatic Hyperplasia in the United Kingdom with Different Assumptions

Exposure	No of Events	PYs	Incidence Rate 95% CI, (per 1000 PYs)	Crude HR (95% CI)	Adjusted* HR (95% CI)
Vary grace period to 0 day					
Currently not exposed	2494	368,276	6.8 (6.5-7.0)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	894	109,561	8.2 (7.6-8.7)	1.19 (1.11-11.29)	0.93 (0.86-1.01)
Currently exposed to 5αRIs	505	49,822	10.1 (9.3-11.1)	1.48 (1.34-1.63)	0.90 (0.82-0.99)
Vary grace period to 90 days					
Currently not exposed	2144	335,073	6.4 (6.1-6.7)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	1149	134,339	8.6 (8.1-9.1)	1.33 (1.24-1.43)	1.01 (0.94-1.09)
Currently exposed to 5αRIs	600	58,248	10.3 (9.5-11.2)	1.59 (1.46-1.75)	0.94 (0.86-1.04)
Censoring patients with surgical interventions of the prostate during the follow-up					
Currently not exposed	1899	304,470	6.2 (6.0-6.5)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	987	118,850	8.3 (7.8-8.8)	1.32 (1.22-1.43)	0.98 (0.91-1.06)
Currently exposed to 5αRIs	522	51,331	10.2 (9.3-11.1)	1.63 (1.48-1.79)	0.93 (0.84-1.03)
Patients with cardiovascular disease at baseline (n = 23,088)					
Currently not exposed	1249	65,026	19.2 (18.2-20.3)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	654	31,026	21.1 (19.5-22.8)	1.09 (0.99, 1.20)	1.03 (0.93-1.13)
Currently exposed to 5αRIs	366	15,340	23.9 (21.5-26.4)	1.26 (1.12, 1.41)	1.01 (0.90-1.14)
Patients without cardiovascular disease at baseline (n = 71,352)					
Currently not exposed	997	281,166	3.6 (3.3-3.8)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	413	94,551	4.4 (4.0-4.8)	1.24 (1.10-1.39)	0.94 (0.84-1.06)
Currently exposed to 5αRIs	214	40,551	5.3 (4.6-6.0)	1.39 (1.19-1.61)	0.83 (0.71, 0.97)
Excluded patients with a history of hypertension at baseline (n = 59,219)					
Currently not exposed	1064	246,048	4.3 (4.1-4.6)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	385	74,548	5.2 (4.7-5.7)	1.19 (1.06-1.33)	0.97 (0.86-1.09)
Currently exposed to 5αRIs	234	33,435	7.0 (6.2-8.0)	1.55 (1.34-1.78)	0.96 (0.83-1.11)
Exposure to selective α-blockers (BPH) vs non-selective (BPH + hypertension)†					
Currently not exposed	2231	345,800	6.5 (6.2-6.7)	1.00 (Reference)	1.00 (Reference)
Currently exposed to selective α-blockers	846	104,090	8.1 (7.6-8.7)	1.25 (1.15, 1.35)	0.99 (0.91-1.07)
Currently exposed to non-selective α-blockers	191	19,624	9.7 (8.5-11.2)	1.50 (1.29-1.74)	1.02 (0.88-1.18)
Currently exposed to 5αRIs	571	55,324	10.3 (9.5-1.2)	1.59 (1.45-1.74)	0.94 (0.86-1.04)
As-treated analysis					
Currently not exposed	1261	218,395	5.8 (5.5, 6.1)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	192	24,594	7.8 (6.8, 9.0)	1.19 (1.01-1.39)	0.87 (0.74-1.03)
Currently exposed to 5αRIs	77	5,095	15.1 (12.1, 18.9)	2.34 (1.85-2.96)	1.09 (0.86-1.39)
Censoring patients with prescriptions of propecia					
Currently not exposed	2245	346,100	6.5 (6.2-6.8)	1.00 (Reference)	1.00 (Reference)
Currently exposed to α-blockers	1067	125,559	8.5 (8.0-9.0)	1.30 (1.21-1.40)	1.00 (0.93-1.07)
Currently exposed to 5αRIs	578	55,739	10.4 (9.6-11.3)	1.58 (1.44-1.73)	0.94 (0.86-1.03)
Hospitalization for heart failure defined by only HES	3590	527,660	6.80 (6.58-7.03)		
Currently not exposed	2055	346,192	5.94 (5.68-6.20)	1 (Reference)	1 (Reference)
Currently exposed to α-blockers	989	125,577	7.88 (7.40-8.38)	1.32 (1.22-1.42)	1.01 (0.93-1.09)
Currently exposed to 5αRIs	546	55,891	9.77 (8.98-10.62)	1.63 (1.48-1.79)	0.96 (0.87-1.06)
Heart failure defined by ONS (causes of death)	999	535,459	1.87 (1.75-1.98)		
Currently not exposed	634	350,781	1.81 (1.67-1.95)	1 (Reference)	1 (Reference)
Currently exposed to α-blockers	214	127,461	1.68 (1.47-1.92)	0.93 (0.80-1.09)	0.71 (0.61-0.83)
Currently exposed to 5αRIs	151	57,217	2.64 (2.25-3.10)	1.40 (1.17-1.67)	0.78 (0.65-0.93)
Hospitalization for heart failure	3893	527,660	7.38 (7.15-7.61)		
Currently not exposed	2246	346,192	6.49 (6.22-6.76)	1 (Reference)	1 (Reference)
Currently exposed to α-blockers only	1067	125,577	8.50 (8.00-9.02)	1.30 (1.21-1.40)	1.00 (0.92-1.07)
Currently exposed to 5αRIs only	376	30,287	12.41 (11.22-13.74)	1.90 (1.70-2.12)	1.02 (0.91-1.14)
Currently exposed to α-blockers and 5αRIs	204	25,604	7.97 (6.95-9.14)	1.21 (1.05-1.40)	0.82 (0.71-0.95)

5αRIs = 5-alpha reductase inhibitors; α-blockers = alpha-blockers; CI = confidence interval; HES = hospital episodes statistics; HR = hazard ratios; ONS = Office of National Statistics; PYs = person-years.

*Adjusted for age, calendar year, region, IMD, lifestyle variables (body mass index, alcohol, and smoking), number of general practitioner visits, number of hospitalizations, number of drug classes, surgical interventions for benign prostatic hyperplasia, Charlson Comorbidity Index, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, type 2 diabetes, hypertension, dyslipidemia, depression, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction, previous stroke, sleep apnea, cancers other than prostate cancer, acetylsalicylic acid, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antidepressants, beta-blockers, calcium-channel blockers, diuretics, fibrates, smoking cessation drugs, non-steroidal anti-inflammatory drugs, and statins. Missing data for Index of Multiple Deprivation, body mass index, and smoking were imputed using multiple imputation.

†Non-selective α-blockers are prescribed for both BPH and hypertension.