5-Alpha Reductase Inhibitors and the Risk of Anemia among Men with Benign Prostatic Hyperplasia: A Population-based Cohort Study

Short title: 5-Alpha Reductase Inhibitors and the Risk of Anemia

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ABSTRACT

Background: 5-alpha reductase inhibitors (5αRIs) are effective for the treatment of benign prostatic hyperplasia (BPH). However, 5αRIs could lower levels of hemoglobin, increasing the risk of anemia.

Objective: To compare the rate of anemia between new users of 5αRIs and α-blockers in the United Kingdom (UK).

Methods: We conducted a matched, active comparator, new-user cohort study using the Clinical Practice Research Datalink. The study population consisted of men aged 40+ years with incident BPH who initiated 5αRIs between 1998 and 2019 and were matched 1:1 on propensity score to new users of α-blockers. Anemia was defined by a measured hemoglobin < 130 g/l. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for anemia.

Results: Our study cohort included 9,429 new users of 5αRIs and 9,429 matched new users of α-blockers. Their median durations of follow-up were 136 days (interquartile range [IQR]: 54-336 days) and 77 days (IQR: 58-236), respectively. A total of 2,865 5αRIs users and 2,407 α-blocker users developed incident anemia, representing rates of 37.3 (95% CI: 33.6-41.3) and 42.0 (95% CI: 38.1-46.2) per 100 person-years, respectively. The use of 5αRIs was not associated with an increased risk of anemia compared to the use of α-blockers (HR: 0.95, 95% CI: 0.90-1.00). Similarly, we did not observe an increased risk of mild, moderate, or severe anemia.

Conclusion: The use of 5αRIs was not associated with an increased risk of anemia compared to the use of α-blockers among men with BPH.

Keywords: 5αRIs, α-blockers, Benign prostatic hyperplasia, Anemia, Hematology

What is already known about this subject?

- 5-alpha-reductase inhibitors and α-blockers are widely prescribed to manage the symptoms of BPH.
- Despite a strong biological rationale supporting an association between 5αRIs and anemia, only a small number of studies have assessed this risk.
- Previous studies reported an association between the use of finasteride and lowered hemoglobin and hematocrit levels in men with advanced prostate cancer.
- However, the generalizability of this association in men with BPH without cancer is unclear.

What does this study add?

- In our propensity-score-matched, active comparator, new-user cohort study, we observed no increased risk of anemia associated with the use of 5αRIs compared to the use of α-blockers among men with BPH.
- The results of this study, therefore, provide important reassurance regarding the safety of 5αRIs among men with BPH with respect to anemia.

BACKGROUND

5-alpha reductase inhibitors (5αRIs) are a class of drugs prescribed to men with benign prostatic hyperplasia (BPH).[1] They relieve the symptoms of BPH by reducing prostate size by 20-30% within 3-6 months of use.[2] Randomized controlled trials demonstrated that 5αRIs reduce the risk of acute urinary retention by 50% and reduce the risk of surgery by 48% in comparison to placebo.[3] They have also been shown to improve quality of life.[4]

Biological rationale exists linking the use of 5αRIs with a potential increased risk of anemia. By inhibiting the 5α-reductase enzyme, 5αRIs lower levels of the active testosterone metabolite dihydrotestosterone [5], which may increase the risk of anemia. Testosterone stimulates erythropoiesis in adults, increasing hemoglobin levels by 1-2 g/dL.[6] However, endogenous serum testosterone levels decline as men age and this, in turn, increases the risk of anemia in older men.[7,8] Moreover, men with hypogonadism and those taking antiandrogenic drugs frequently have anemia.[9-11] In contrast, men with exogenous testosterone replacement therapy or diseases characterized by high testosterone have increased hemoglobin levels.[12-15] Anemia is associated with a poorer quality of life, worse outcomes, and increased mortality. In approximately one-third of older adults with anemia, the cause is unknown.[16]

Despite a strong biological rationale supporting an association between 5αRIs and anemia, only a small number of studies have assessed this risk. One study reported that finasteride lowered hemoglobin and hematocrit levels in men with advanced prostate cancer,[9] and another reported a decline in hemoglobin levels after three months of use of finasteride and other androgen deprivation therapy in metastatic prostate cancer patients.[17] Nevertheless, these observational studies had potential methodological limitations, including inadequate control of confounding[17-19] and potential immortal time bias.[9] Furthermore, both studies were conducted in

cancer patients, and the generalizability of their results to patients with BPH is unclear. Our objective was therefore to compare the rate of anemia with 5αRIs to that with α-blockers among men with incident BPH.

METHODS

Data sources

We conducted a retrospective cohort study using an active comparator, new-user design[20] using the United Kingdom's (UK's) Clinical Practice Research Datalink (CPRD) Gold[21]. The CPRD contains the complete primary care medical records of over 14 million patients from more than 700 general practices across the UK.[22] It covers approximately 11% of the UK population, and it is broadly representative of the age, sex, and ethnicity of the UK population.[22] The CPRD contains demographic information, lifestyle information, and data regarding primary care, including clinical events, use of preventive care, tests, immunizations, specialist referrals, reports of hospital admissions, and deaths.[21] Clinical diagnoses are recorded using Read codes, a hierarchical clinical classification system containing over 96,000 codes.[22] The CPRD prescriptions, generated by the general practitioner, are recorded using drug product and British National Formulary codes.[21] CPRD data have been previously validated and are of high quality.[23]

This study underwent scientific and ethical review by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (ISAC number 19_150A2) and by the research ethics board of the Jewish General Hospital in Montreal, Canada (JGH 17-008). The study is reported following the STROBE guideline (Supplementary Table 1).

Data Availability Statement

The data that support the findings of this study were obtained from the CPRD. Restrictions apply to the availability of these data, which were used under license for this study.

Study population

We first created a base cohort of all men aged ≥40 years in the CPRD with incident BPH between January 1st, 1998, and February 20th, 2019. The date of this BPH diagnosis defined base cohort entry. We excluded patients who received prescriptions for both 5αRIs and α-blockers before base cohort entry and men with less than one year of recorded history in the CPRD at the time of base cohort entry to ensure sufficient observation time to assess incident BPH and measure comorbidities and other potential confounders. From this base cohort, we constructed our study cohort, which included all men with BPH with new use of 5αRIs or α-blockers, with new use defined by no previous prescription for either drug class in the previous 365 days. The prescription date of this new prescription defined the study cohort entry. We excluded patients who received prescriptions for both 5αRIs and α-blockers on the day of study cohort entry. In addition, we excluded patients with a diagnosis of prostate cancer any time before study cohort entry, as 5αRIs may be used off-label in these patients.[24] We also excluded any patient with a diagnosis of anemia or hemoglobin measurement below 130 g/l in the 12 months before study cohort entry. We did not consider Propecia® when assessing 5αRIs, as this formulation of finasteride is used to treat male pattern baldness.[25] In all analyses, we followed patients from cohort entry until the occurrence of a study endpoint (defined below) or censoring due to discontinuation of the study medication, the addition of or switching to another BPH medication (from 5αRI to α-blocker or vice versa), death, a diagnosis of prostate cancer, departure from the CPRD, or the end of the study period (February 20th, 2019), whichever occurred first. (Supplementary Figure 1)

Exposure

The primary exposure definition used an as-treated approach, a time-fixed approach in which exposure was defined by the cohort-entry defining treatment (5αRIs or α-blockers) and patients were considered continuously exposed from initiation until the initiation of another BPH drug (including combination therapy) or drug discontinuation. Drug discontinuation was defined by a treatment gap of at least 30 days between the end of one prescription and the beginning of the next. The 30-day grace period was used to account for the biological half-life of the medication and non-adherence.

We matched 5αRI new-users to α-blocker new-users on propensity score (described below). New-users of α-blockers were selected as our reference group as the use of an active comparator can reduce confounding by indication and by other variables,[20] and there is no available evidence to suggest that the use of α-blockers is associated with the risk of anemia. We restricted inclusion to selective α-blockers that are solely prescribed for BPH (alfuzosin, silodosin, and tamsulosin), excluding those also prescribed for the treatment of hypertension (doxazosin, indoramin, prazosin, and terazosin).

Outcome

The primary endpoint was new anemia, defined by a recorded hemoglobin measurement below 130 g/l, as defined by the World Health Organization criteria.[26] We did not include diagnostic codes (i.e., Read codes) for anemia as part of our primary outcome definition to allow for the assessment of anemia severity. The date of the laboratory test defined the event date. As a secondary outcome, we sub-classified anemia by severity using the WHO criteria for mild (110-129 g/l), moderate (80-109 g/l), and severe (<80g/l) anemia.[26]

Covariates

Prespecified potential confounders included demographic characteristics (e.g., age), time variables (e.g., study cohort entry year), lifestyle variables (e.g., BMI, smoking status), and prostate-specific antigen (PSA) levels (closest measurement before study cohort entry). We also assessed conditions known to increase the risk of anemia (myelodysplastic syndromes, chronic obstructive pulmonary disease, chronic kidney disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, history of bleeding; measured at any time before cohort entry), surgery (measured in the 3 months before study cohort entry), previous cancer diagnoses (excluding non-melanoma skin cancers), previous chemotherapy, and previous radiation therapy. In addition, we assessed the use of pharmacological agents known to increase the risk of bleeding (warfarin, vitamin K antagonists (VKA), direct oral anticoagulants (DOACs), antiplatelet agents, and selective serotonin reuptake inhibitors; measured in the year before study cohort entry). We measured the number of prescriptions issued and the number of visits to the general practitioners, proxies for overall health. Finally, we computed the Deyo version of the Carlson Comorbidity Index [27-30]. We defined the comorbidities using Read Codes in the CPRD recorded any time before study cohort entry, and prescriptions were defined using British National Formulary codes in the year before study cohort entry.

Statistical analysis

We generated descriptive statistics at the time of study cohort entry using counts and their proportions. We used logistic regression to estimate the probability of receiving 5αRIs versus α-blockers at study cohort entry. This propensity score model included all covariates listed above as predictors of the exposure without further variable selection.[31] Missing values were included in this model through the use of indicator variables. Model fit was assessed using the c-statistic. New users of 5αRIs were matched to new users of α-blockers using the nearest neighbor

approach without replacement. Balance of covariates was assessed before and after matching using the absolute value of the standardized difference, with a difference of less than 0.1 considered to be negligible.

Within the matched cohort, we estimated the rate of anemia per 100 person-years (PYs) and corresponding 95% confidence intervals (CIs) overall and by treatment group using Poisson regression. We used a Cox proportional hazards model to estimate the hazard ratio (HR) and 95% CI for anemia with 5αRIs versus α-blockers. Plots of Schoenfeld residuals were used to visually assess the proportionality of hazards.[32]

We conducted three secondary analyses. First, we assessed the risk of anemia separately for different categories of anemia severity: mild (110-129 g/l), moderate (80-109 g/l), and severe (<80 g/l) anemia based on the WHO criteria.[26] Second, we sub-classified 5αRI use by molecule (dutasteride or finasteride). Finally, we investigated the potential presence of a duration-response relationship between the current use of 5αRIs and anemia according to five pre-specified durations of continuous use: <6, 6-12, 13-18, 19-24, and ≥ 25 months.

To assess the robustness of our results, we conducted nine sensitivity analyses. First, we repeated the primary analysis using an intention-to-treat exposure definition and a maximum follow-up of 3, 6, 9, and 12 months. Second, more frequent PSA testing among 5αRI users than among α-blockers users could introduce detection bias. To assess the potential of detection bias, we employed a stricter cohort entry criteria that required patients to have at least two hemoglobin results in the normal range in a year before study cohort entry. In this subpopulation, we assumed that the subsequent hemoglobin measurements after cohort entry would be non-differential. Third, to further assess the effect of detection bias, we censored patients after one year of follow-

up with no hemoglobin measurements. Fourth, we repeated the primary analysis without excluding patients with an episode of anemia (a diagnosis for anemia, an abnormal hemoglobin measurement, or a treatment or procedure for anemia) in the year before cohort entry. Fifth, to assess potential outcome misclassification, we expanded our outcome definition to also include a CPRD Read code for anemia or receipt of anemia-related treatments or procedures (including iron supplements, folic acid, vitamin B12, and erythropoietin). Six, we varied our grace period to 0 and 90 days. Seventh, we restricted the study period to 2003-2019 since dutasteride was not available in the UK until 2003. Eighth, patients were required to have two consecutive prescriptions of the study medication to enter the study cohort. In this sensitivity analysis, cohort entry was defined by the date of the second prescription. Finally, cancer can increase the risk of anemia. Hence, we excluded all men with a history of cancer before cohort entry.

All data management and analyses were conducted with the Aetion Evidence Generation Platform (AEP) using the Safety Evaluation Application, version r4.2.20200319_1912.[33] In AEP, the statistical computations were conducted using R version 3.4.2 (2018-01-25).[34]

RESULTS

The CPRD included 140,738 patients with an incident diagnosis of BPH between January 1, 1998 and February 20, 2019 (Figure 1). After the application of the inclusion and exclusion criteria, 62,380 patients were included in the study cohort (9,433 exposed to 5αRIs and 52,947 exposed to α-blockers). Following propensity score matching, 9,429 patients were included in each treatment group.

Table 1 presents the baseline characteristics of the study cohort before and after propensity score matching. There were several notable differences between groups before matching. In comparison to the new users of α-blockers, new users of 5αRIs were older and had higher PSA levels. In addition, they were more likely to have a history of CKD, COPD, cancer, GI ulcer, bleeding, hemorrhage, myelodysplastic syndrome, and Charlson comorbidity index score ≥ 2. New users of 5αRIs were also more likely to prescribed antiplatelet and anticoagulant (VKA or DOAC) therapy than α-blockers users. After matching on the propensity score, no important differences in baseline characteristics were present, with all standardized differences less than 0.1 (Table 1, Supplementary Figure 2, and Supplementary Table 2). The c-statistics for the propensity score model within each propensity score decile was less than 0.6 (Supplementary Table 3). The median age of patients was 72 years with IQR (65-78 years). After matching, similar proportions of 5αRIs and α-blockers patients had histories of BMI ≥ 30 kg/m^2 (11.7% vs 11.9%), PSA ≥ 20 ng/ml (1.9% vs. 1.8%), cancer (18.1% vs. 18.0%), and surgery (1.5% vs. 1.6%) (Table 1).

Table 2 summarizes the follow-up information of the propensity score-matched cohort. The median duration of follow-up was 136 days (IQR: 54-336 days) among new-users of 5αRIs

and 77 days (IQR: 58-236 days) among new users of α-blockers. A total of 2,865 new users of 5αRIs and 2,407 new users of α-blockers developed anemia, representing rates of 37.3 (95% CI: 35.9-38.7) and 40.5 (95% CI: 38.9-42.2) per 100 PYs, respectively (Table 2).

Figure 2 and Table 2 present the results of our primary and secondary analyses. Compared with the new use of α-blockers, the new use of 5αRIs was not associated with an increased risk of anemia among men with BPH (HR: 0.95, 95% CI: 0.90-1.00). The Schoenfeld residual plot showed the adequate convergence of the Cox proportional hazards model (Supplementary Figure 3). Analyses by anemia severity revealed no association between 5αRIs versus α-blockers and the risks of severe (HR: 0.97, 95% CI: 0.92-1.03), moderate (HR: 1.08, 95% CI: 0.83-1.42), or mild (HR: 1.12, 95% CI: 0.95-1.32) anemia. No differences in anemia risk were observed by 5αRI molecules. No clear duration-response pattern was present (Figure 2 and Table 2).

Our nine sensitivity analyses produced results that were consistent with those of our primary analysis (Figure 3 and Supplementary Table 4).

DISCUSSION

Our propensity-score-matched, active comparator, new-user cohort study was designed to examine the association between 5αRIs and the risk of anemia among men with BPH. We observed no increased risk of anemia with 5αRIs versus α-blockers in this study population. Similar results were observed for mild, moderate, and severe anemia and for the individual 5αRI molecules. No clear duration-response pattern was observed. Consistent results were obtained across several sensitivity analyses, suggesting that our results were robust to study assumptions.

The pathophysiology of anemia is diverse and multifactorial, with potential causes including genetic mutations, blood loss, malnutrition, altered red blood cell morphology, infectious processes, or chronic inflammation.[35] The global burden of anemia is high,[36] causing 61.5 (41.0–88.7) million years lived with disability and affecting 1.93 billion people in 2013.[36] Health consequences of anemia include a predisposition to infection[37] and heart failure.[38] It is also associated with a poorer quality of life[39] and substantial health care cost.[40] Our real-world study provides important reassurance with respect to the safety of 5αRIs concerning this clinically important endpoint.

Several previous studies described the potential association between antiandrogenic therapies and the risk of anemia. Hicks et.al. reported an increased risk of anemia in patients with prostate cancer prescribed androgen deprivation therapy (HR: 2.90, 95% CI: 2.67-3.16).[11] However, this particular study did not examine the anemia risk associated with 5αRIs specifically. Ornstein et al. found that finasteride lowered hemoglobin and hematocrit levels among men with advanced prostate cancer,[9] and Beer et al. reported a decline in hemoglobin levels after three months of finasteride and other androgen deprivation therapy.[17] Nevertheless, these studies had several potential limitations, including inadequate control of confounding[18,19]

and potential immortal time bias[9]. Furthermore, all three studies were conducted in cancer patients, and the generalizability of their results to patients with BPH is unclear. The other possible explanation for the observed estimate against our hypothesis could be that 5αRIs are less potent than androgen deprivation therapy. A previous study demonstrated that androgen deprivation therapy increased plasma hormone levels in a dose-dependent manner in comparison to 5αRIs.[41]

Our study has several strengths. To our knowledge, this is the largest observational study to have directly compared the risk of anemia between 5αRIs and α-blockers users among men with BPH. Second, we used the CPRD, one of the largest population-based longitudinal primary care data sources. With our use of data from routine general practice care in the UK, our study is likely generalizable to patients treated in a real-world setting.[22] Third, with the use of a new-user active comparator study design, we minimized potential confounding while eliminating prevalent-user bias.[42] Fourth, we matched on a propensity score that included several prespecified potential confounders, further minimizing potential confounding.[43]

This study also has potential limitations. First, we included missing data using an indicator variable rather than multiple imputation, which may have resulted in some model misspecification in our propensity score. Second, a substantial number of patients were censored before reaching the anemia endpoint (Supplementary Table 5), and selection bias due to informative censoring is possible. However, we observed similar estimates in our sensitivity analysis using an intention-to-treat exposure definition with 3, 6, 9, or 12 months of follow-up. Third, the CPRD records prescriptions issued, but it does not include information about dispensing or adherence. Exposure misclassification is therefore possible. Finally, patients on 5αRIs may be more likely to undergo PSA testing than patients on α-blockers.[44] This increased

blood testing during routine follow-up among patients with 5αRIs may increase the probability of detecting anemia in this group, resulting in detection bias. For this reason, we conducted a sensitivity analysis in which we strictly defined cohort entry requiring patients to have at least two hemoglobin results in the normal range in a year before cohort entry and censored patients after one year with no hemoglobin measurements. These analyses produced results that were consistent with those of our primary analysis, suggesting that detection bias was unlikely in this study.

CONCLUSIONS

In our propensity-score-matched, active comparator, new-user cohort study, we observed no increased risk of anemia associated with the use of 5αRIs compared to the use of α-blockers among men with BPH. No clear duration-response pattern was observed. The results of this study, therefore, provide important reassurance regarding the safety of 5αRIs among men with BPH with respect to anemia.

DISCLOSURES

Dr. Ayele is an employee of Merck. Finasteride, one of the 5αRIs, which is sold under the brand name Proscar is the product of Merck. Dr. Ayele conducted this research during his post-doctoral training at McGill University prior to his employment at Merck. The remaining authors have no relationships to disclose.

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AUTHORS' CONTRIBUTION

HTA designed the study, drafted the protocol, analyzed the data, and drafted the manuscript. KBF contributed to study design, interpreted the data, critically reviewed the manuscript for important intellectual content, and supervised the study. AD contributed to the study design, interpreted the data, and critically reviewed the manuscript for important intellectual content. All authors approved the final version of the manuscript. KBF is a guarantor.

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Table 1. Characteristics of new users of 5αRIs and α-blockers among men with incident benign prostatic hyperplasia, before and after propensity score matching.

Patients characteristics	Overall cohort (n=62,380)	Before matching			After propensity score matching		
		α-blockers (n=52,947)	5αRIs (n=9,433)	Standardized Difference	α-blockers (n=9,429)	5αRIs (n=9,429)	Standardized Difference
Age in years							
≤55, n (%)	6,707 (10.8)	6,179 (11.7)	528 (5.6)	6.1	529 (5.6)	528 (5.6)	0.0
56 - 65, n (%)	17,968 (28.8)	15,897 (30.0)	2,071 (22.0)	8.1	2,089 (22.2)	2,071 (22.0)	0.01
66 - 75, n (%)	21,720 (34.8)	18,240 (34.4)	3,480 (36.9)	-2.4	3,481 (36.9)	3,480 (36.9)	0.0
76 - 84, n (%)	12,692 (20.3)	10,111 (19.1)	2,581 (27.4)	-8.3	2,572 (27.3)	2,580 (27.4)	-0.1
≥ 85, n (%)	3,293 (5.3)	2,520 (4.8)	773 (8.2)	-3.4	758 (8.0)	770 (8.2)	-0.1
Body mass index (kg/m^2)							
< 30, n (%)	18,068 (29.0)	15,120 (28.6)	2,948 (31.3)	-2.7	2,946 (31.2)	2,946 (31.2)	0.01
≥ 30, n (%)	7,346 (11.8)	6,226 (11.8)	1,120 (11.9)	-0.1	1,106 (11.7)	1,120 (11.9)	0.01
Missing, n (%)	36,966 (59.3)	31,601 (59.7)	5,365 (56.9)	2.8	5,377 (57.0)	5,363 (56.9)	0.01
Smoking status							
Current smoker, n (%)	8,103 (13.0)	7,002 (13.2)	1,101 (11.7)	1.5	1,069 (11.3)	1,100 (11.7)	0.02
Non-smoker, n (%)	28,162 (45.1)	23,933 (45.2)	4,229 (44.8)	0.4	4,286 (45.5)	4,227 (44.8)	0.02
Past smoker, n (%)	24,086 (38.6)	20,306 (38.4)	3,780 (40.1)	-1.7	3,754 (39.8)	3,779 (40.1)	0.02
Missing, n (%)	2,029 (3.3)	1,706 (3.2)	323 (3.4)	-0.2	320 (3.4)	322 (3.4)	0.02
Prostatic specific antigen (ng/ml)							
< 4, n (%)	24,361 (39.1)	21,167 (40.0)	3,194 (33.9)	6.1	3,254 (34.5)	3,194 (33.9)	0.015
4 - 10, n (%)	8,104 (13.0)	6,558 (12.4)	1,546 (16.4)	-4.0	1,554 (16.5)	1,546 (16.4)	0.015
10 - 20, n (%)	2,001 (3.2)	1,448 (2.7)	553 (5.9)	-3.1	550 (5.8)	550 (5.8)	0.015
≥ 20, n (%)	757 (1.2)	577 (1.1)	180 (1.9)	-0.8	169 (1.8)	179 (1.9)	0.015
Missing, n (%)	27,157 (43.5)	23,197 (43.8)	3,960 (42.0)	1.8	3,902 (41.4)	3,960 (42.0)	0.015
Visits to the general practitioner in the year before cohort entry							
≤ 5, n (%)	41,909 (67.2)	35,934 (67.9)	5,975 (63.3)	4.5	5,958 (63.2)	5,974 (63.4)	0.02
6 – 9, n (%)	9,050 (14.5)	7,576 (14.3)	1,474 (15.6)	-1.3	1,522 (16.1)	1,474 (15.6)	0.02
≥ 10, n (%)	11,421 (18.3)	9,437 (17.8)	1,984 (21.0)	-3.2	1,949 (20.7)	1,981 (21.0)	0.02
Number of prescriptions issued in the year before cohort entry							
< 5; n (%)	14,597 (23.4)	12.707 (24.0)	1,821 (19.3)	4.7	1,905 (20.2)	1,820 (19.3)	0.05
5 - 9; n (%)	6675 (10.7)	5665 (10.7)	943 (10.0)	0.7	962 (10.2)	952 (10.1)	0.05
≥ 10; n (%)	41,046 (65.8)	34,521 (65.2)	6,660 (70.6)	-5.3	6,572 (69.7)	6,557 (70.6)	0.05
Devo version of Charleston Comorbidity Index (CCI)							
0; n (%)	51,262 (82.2)	43,753 (82.6)	7,509 (79.6)	3.0	7,488 (79.4)	7,506 (79.6)	0.014

1; n (%)	8,423 (13.5)	6,998 (13.2)	1,425 (15.1)	-1.9	1,412 (15.0)	1,424 (15.1)	0.014
≥ 2; n (%)	2,695 (4.3)	2,196 (4.1)	499 (5.3)	-1.1	529 (5.6)	499 (5.3)	0.014
CKD, n (%)	5,225 (8.4)	4,173 (7.9)	1,052 (11.2)	-3.3	1,092 (11.6)	1,050 (11.1)	0.01
COPD, n (%)	7,998 (12.8)	6,711 (12.7)	1,287 (13.6)	-1.0	1,258 (13.3)	1,286 (13.6)	0.01
Bleeding & hemorrhage,[$] n (%)	24,985 (40.0)	20,543 (38.8)	4,442 (47.1)	-0.3	4,436 (47.1)	4,432 (47.0)	0..02
Myelodysplastic syndrome, n (%)	79 (0.1)	61 (0.1)	18 (0.2)	-0.1	19 (0.2)	18 (0.2)	0.002
Cancer other than skin cancer, n (%)	10,309 (16.5)	8,600 (16.2)	1,709 (18.1)	-1.9	1,700 (18.0)	1,707 (18.1)	0.002
Previous chemotherapy, n (%)	1,060 (1.7)	882 (1.7)	178 (1.9)	-0.2	207 (2.2)	178 (1.9)	0.02
Previous radiation therapy, n (%)	471 (0.8)	402 (0.8)	69 (0.7)	0.0	70 (0.7)	69 (0.7)	0.001
Anti-platelet therapy,[#] n (%)	18,531 (29.7)	15,169 (28.6)	3,362 (35.6)	-0.8	3,350 (35.5)	3,356 (35.6)	0.00
Rheumatoid arthritis, n (%)	801 (1.3)	682 (1.3)	119 (1.3)	0.0	150 (1.6)	119 (1.3)	0.03
Surgery, n (%)	944 (1.5)	806 (1.5)	138 (1.5)	0.1	149 (1.6)	138 (1.5)	0.01
SSRI, n (%)	9,974 (16.0)	8,686 (16.4)	1,288 (13.7)	2.8	1,254 (13.3)	1,287 (13.6)	0.01
VKA or DOAC, n (%)	3,482 (5.6)	2,730 (5.2)	752 (8.0)	-2.8	704 (7.5)	750 (8.0)	0.02

5αRIs: Five Alpha Reductase Inhibitors; **α-blockers**: Alpha-Blockers; **ASA**: Acetyl Cyclic Acid; **CCI**: Charleston Comorbidity Index; **CI**: Confidence Interval; **CKD**: Chronic Kidney Diseases; **COPD**: Chronic Obstructive Pulmonary Diseases; **DOAC**: Direct Oral Anticoagulant; **IQR**: Interquartile Range; **GI**: Gastrointestinal; **n**: Number; **SD**: Standard Deviation; **SSRI**: Selective Serotonin Reuptake Inhibitors; **VKA**: Vitamin K Antagonist; [$] Includes gastrointestinal ulcer, bleeding, hemorrhage, genitourinary bleeding or hematuria, or bleeding disorders; [#] Includes low-dose acetylsalicylic acid (ASA).

Table 2. Association between the use of 5αRIs versus α-blockers and the risk of anemia among men with benign prostatic hyperplasia in the United Kingdom.

Types of analyses	Exposure	Cohort size[$]	Median days of follow-up (IQR)	Person -years	Number of Anemia	Rate of anemia per 100 person-years (95% CI)	HR* (95% CI)
Primary analysis	5αRIs	9,429	136 (54, 336)	7,684	2,865	37.3 (35.9, 38.7)	0.95 (0.90, 1.00)
	α-blockers	9,429	77 (30-236)	5,940	2,407	40.5 (38.9, 42.2)	1.00 (Reference)
Secondary analyses							
Anemia severity							
Mild anemia (Hb 110-129 g/l)	5αRIs	9,424	191 (60, 577)	12,620	371	2.94 (2.65, 3.26)	1.12 (0.95, 1.32)
	α-blockers	9,424	97 (28, 348)	8,790	230	2.62 (2.29, 2.98)	1.00 (Reference)
Moderate anemia (Hb 80-109 g/l)	5αRIs	9,424	195 (61, 587)	12,959	139	1.07 (0.90, 1.27)	1.08 (0.83, 1.42)
	α-blockers	9,424	99 (28, 357)	8,962	87	9.71[#] (7.78, 11.97)	1.00 (Reference)
Severe anemia (Hb <80 g/l)	5αRIs	9,427	142 (54, 348)	8,036	2,576	32.06 (30.83, 33.32)	0.97 (0.92, 1.03)
	α-blockers	9,427	79 (28, 245)	6,135	2,148	35.01 (33.55, 36.52)	1.00 (Reference)
Molecular subclasses of 5αRIs							
Dutasteride (5αRIs) versus α-blockers	5αRIs	1,613	119 (44, 316)	1,170	531	45.38 (41.61, 49.41)	0.99 (0.88, 1.12)
	α-blockers	1,613	85 (28, 267)	1,066	487	45.68 (41.72, 49.93)	1.00 (Reference)
Finasteride (5αRIs) versus α-blockers	5αRIs	8,214	138 (54, 337)	6,751	2,450	36.29 (34.87, 37.76)	0.87 (0.82, 0.93)
	α-blockers	8,214	79 (28, 244)	4,991	2,075	41.57 (39.81, 43.40)	1.00 (Reference)
Continuous duration of use							
< 6 months	5αRIs	5,695	54 (26, 101)	1,069	688	64.36 (59.64, 69.35)	0.98 (0.88, 1.10)
	α-blockers	5,695	43 (28, 72)	930	609	65.48 (60.39, 70.90)	1.00 (Reference)
6-12 months	5αRIs	7,094	217 (168, 273)	3,997	2,034	50.89 (48.70, 53.15)	0.95 (0.89, 1.01)
	α-blockers	7,094	217 (174, 273)	3,917	2,105	53.74 (51.47, 56.09)	1.00 (Reference)
12-18 months	5αRIs	4,457	379 (187, 443)	3,935	1,770	44.98 (42.91, 47.13)	0.99 (0.93, 1.06)
	α-blockers	4,457	385 (210, 446)	3,913	1,776	45.39 (43.30, 47.55)	1.00 (Reference)
18-24 months	5αRIs	3,078	534 (180, 614)	3,483	1,511	43.38 (41.22, 45.63)	1.05 (0.98, 1.13)
	α-blockers	3,078	550 (213, 622)	3,504	1,441	41.12 (39.03, 43.30)	1.00 (Reference)
≥24 months	5αRIs	6,837	525 (170, 965)	12,932	4,225	32.67 (31.69, 33.67)	0.99 (0.94, 1.03)

	α-blockers	6,837	635 (188, 1,027)	12,378	4,100	33.12 (32.12, 34.15)	1.00 (Reference)

* Baseline confounders included in the propensity score model: Year of cohort entry, age, body mass index, smoking status, prostate-specific antigen, Charlson comorbidity index, patients' visit to the general practitioner, number of prescriptions issued, chronic kidney disease, chronic obstructive pulmonary disease, gastrointestinal ulcer, gastrointestinal bleeding or hemorrhage, myelodysplastic syndrome, cancer other than skin cancer, previous chemotherapy or radiotherapy, anti-platelet therapy, low dose acetylsalicylic acid, rheumatoid arthritis, surgery, selective serotonin reuptake inhibitors, vitamin k antagonist or direct oral anticoagulant

[#] per 1000 person-years; [$] Cohorts matched 1:1 on propensity score**; 5αRIs**: 5 alpha-reductase inhibitors; **CI**: Confidence interval; **Hb**: Hemoglobin; **HR**: Hazard Ratio; **IQR**: Interquartile range.

FIGURE LEGENDS

Figure 1. Construction of study cohort of patients with benign prostatic hyperplasia and new use of 5αRIs or α-blockers. **5αRIs**: Five alpha-reductase inhibitors; **α-blockers**: Alpha-blockers; **BPH**: Benign Prostatic Hyperplasia; **CPRD**: Clinical Practice Research Datalink; **n**: Number.

Figure 2. The risk of anemia with the new use of 5αRIs versus new use of α-blockers among men with benign prostatic hyperplasia. **HR**: Hazard Ratios; **CI**: Confidence Interval; *****Baseline confounders included in the propensity score model: year of cohort entry, age, body mass index, smoking status, prostate-specific antigen, Charlson comorbidity index, visits to the general practitioner in the previous year, number of prescriptions issued, chronic kidney disease, chronic obstructive pulmonary disease, gastrointestinal ulcer, bleeding or hemorrhage, myelodysplastic syndrome, cancer other than skin cancer, previous chemotherapy or radiotherapy, anti-platelet therapy, rheumatoid arthritis, surgery, selective serotonin reuptake inhibitors, and vitamin K antagonist or direct oral anticoagulant.

Figure 3. Sensitivity analyses examining the risk of anemia with the new use of 5αRIs versus new use of α-blockers among men with benign prostatic hyperplasia. **5αRIs**: Five alpha-reductase inhibitors; **α-blockers**: Alpha-blockers; **CI**: Confidence Interval; **HR**: Hazard Ratios; *****Baseline confounders included in the propensity score model: year of cohort entry, age, body mass index, smoking

status, prostate-specific antigen, Charlson comorbidity index, visits to the general practitioner in the previous year, number of prescriptions issued, chronic kidney disease, chronic obstructive pulmonary disease, gastrointestinal ulcer, bleeding or hemorrhage, myelodysplastic syndrome, cancer other than skin cancer, previous chemotherapy or radiotherapy, anti-platelet therapy, rheumatoid arthritis, surgery, selective serotonin reuptake inhibitors, and vitamin K antagonist or direct oral anticoagulant; ****** Censored patients with missing Hemoglobin or no recorded Hemoglobin measurements in 365 days during follow-up.