5-Alpha Reductase Inhibitors and Risk of Kidney and Bladder Cancers in Men with Benign Prostatic Hyperplasia: A Population-Based Cohort Study

Authors and Affiliations: Niamh Doherty[1], Chris R. Cardwell[1], Peter Murchie[2], Christopher Hill[3], Laurent Azoulay[4, 5], Blánaid Hicks[1]

[1.]Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland [2.] School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, Scotland [3.] Regional Nephrology Unit, Belfast City Hospital, Belfast, UK [4.] Centre for Clinical Epidemiology Lady Davis Institute, Jewish General Hospital, Montreal, Canada [5.] Department of Epidemiology, Biostatistics, and Occupational Health and Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada

Running Title: 5-alpha Reductase Inhibitors and Risk of Urological Cancers

Key Words: Benign prostatic hyperplasia, kidney cancer, bladder cancer, 5-alpha reductase inhibitor, epidemiology.

Corresponding Author:
Niamh Doherty
Queens University Belfast, Institute of Clinical Sciences, Block B, Royal Victoria Hospital, Belfast, United Kingdom, BT12 6BA.
Email: ndoherty99@qub.ac.uk
Phone: 028 9097 6350

Financial Support: Dr's B Hicks and CR Cardwell received funding from Cancer Research UK Population Research Fellowship (grant reference 22185). The funder had no role in the study design, analysis, interpretation or writing of the manuscript.

Authors Disclosures: Dr L Azoulay received consulting fees from Janssen and Pfizer for work unrelated to this study.

Word Count: 3,328 (Text: 3,079; Abstract: 249)

Number of Tables: 3

Number of Figures: 2

Abstract

Background: Preclinical evidence suggests that 5-alpha reductase inhibitors, commonly used to treat benign prostatic hyperplasia, are associated with reduced incidence of certain urological cancers, yet epidemiological studies are conflicting. This study aimed to determine whether 5-alpha reductase inhibitors are associated with a reduced risk of kidney and bladder cancers.

Methods: We conducted a new user active-comparator cohort study in the United Kingdom Clinical Practice Research Datalink. From a base cohort of patients with incident benign prostatic hyperplasia, new users of 5-alpha reductase inhibitors and alpha-blockers were identified. Patients were followed-up until a first ever diagnosis of kidney or bladder cancer, death from any cause, end of registration, or 31st December 2017. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals for incident kidney and bladder cancer.

Results: There were 5,414 and 37,681 new users of 5-alpha reductase inhibitors and alpha-blockers, respectively. During a mean follow-up of 6.3 years, we found no association between the use of 5-alpha reductase inhibitors and kidney (adjusted hazard ratio: 1.26, 95% CI 0.74-2.12, n=23) or bladder (adjusted hazard ratio: 0.89, 95% CI 0.64-1.23, n=57) cancer risk compared to alpha-blockers. Similar results were observed across sensitivity analyses.

Conclusions: In this study, we found no association between the use of 5-alpha reductase inhibitors and kidney or bladder cancer incidence in men with benign prostatic hyperplasia when compared to alpha-blocker use.

Impact: The findings of this study indicate that 5-alpha reductase inhibitors are unlikely to reduce kidney or bladder cancer risk.

Introduction

Recommended for the treatment of benign prostatic hyperplasia (BPH), 5-alpha reductase inhibitors (5ARi) act to lower circulating dihydrotestosterone (DHT) by inhibiting the conversion of testosterone to the more potent DHT by 5-alpha reductase enzymes (1). The resulting diminished effect of DHT on the androgen receptor (AR) following 5ARi treatment has been hypothesized to reduce cancer initiation and progression via the hormonal pathway (2). Both kidney and bladder cancer exhibit higher incidence rates in men compared to women (3,4). This observed gender disparity, even when considering important lifestyle factors, has led to increasing interest in determining the role of male sex hormones in initiation and promotion of urological cancers.

The AR is differentially expressed between malignant and benign tissue of both kidney and bladder (5). In addition, *in-vitro* studies demonstrate the downstream effects of AR activation are associated with cell growth and migration in bladder (6-8) and kidney cancer (9). This highlights the importance of the hormonal pathway, especially activity of the AR, in cancer progression in kidney and bladder cancer. Furthermore, treatment with 5ARi was also seen to reduce proliferation of bladder cancer cells (10). Previous observational evidence found reduced incidence of bladder cancer with 5ARi use (11-13), with another study reporting no change in risk of bladder cancer with 5ARi use (14). Only one previous study investigated kidney cancer risk with 5ARi use which found no association (15). However, these studies had some notable limitations including confounding by indication (11,12), exposure misclassification (15), and detection bias (12).

Given the limited observational evidence additional carefully designed observational studies are warranted to determine the effect of lower AR activation from 5ARi treatment on kidney

48 and bladder cancer risk at a population-based level. The active comparator new-user study
49 design offers several advantages in the investigation of drug effects, including in particular
50 the reducing potential confounding by indication (16). Therefore, this population-based
51 cohort study aimed to investigate the risk of kidney and bladder cancer with the use of
52 5ARi's in men with BPH using an active comparator new-user design.

Materials and Methods

Data Source

The Clinical Practice Research Datalink (CPRD) GOLD database is a representative database of electronic health records of over 17 million patients from a network of general practices from throughout the UK (17). Information in the CPRD includes demographics, diagnoses, referrals, and prescriptions, which have been shown to be valid and of high quality (18). Moreover, kidney and urinary tract cancer diagnosis in CPRD were shown to be concordant with the UK National Cancer Data Repository (19). CPRD obtains ethical approval to receive and supply patient data for public health research. The study protocol was approved by the Scientific Advisory Committee of the CPRD (protocol number 18_020).

Study Population

We used an active comparator new user design to compare new users of 5ARi's (finasteride or dutasteride) with new users of alpha-blocker (tamsulosin, alfuzosin, doxazosin, prazosin, or terazosin). Alpha-blockers were chosen as a clinically relevant comparator due to the similar indications of use to 5ARi's, therefore minimising confounding by indication (20). We identified a base cohort of the first 100,000 men diagnosed with BPH between 1st February 1998 and 31st December 2014, who were over the age of 40. From the base cohort we identified all first prescriptions of a 5ARi or alpha-blocker after BPH diagnosis. Cohort entry (T0) was considered as the date of this first prescription. At cohort entry exclusions included those that had prior use of 5ARi or alpha-blocker (prevalent users) any time prior to cohort entry and those with concomitant use of both 5ARi's and alpha-blockers. Additionally, we excluded those with a previous diagnosis of any cancer, and those with less than 1 year of medical history prior to cohort entry. All patients were required to have at least 1 year of

follow-up after cohort entry for latency considerations, to ensure the identification of incident cancer during follow-up and to minimise the impact of reverse causality and detection bias.

Exposure Definition

5ARi and alpha-blocker users were followed using an intention-to-treat approach whereby patients were considered continually exposed to the cohort entry drug from one year after initiation of either 5ARi or alpha-blocker until the end of follow up irrespective of switches, add-ons, or discontinuation. This approach assumes that the effect of exposure on outcome remains after treatment discontinuation. Analyses were conducted for kidney and bladder cancer separately. Thus, we followed up all patients who met the study criteria, from one year after cohort entry until either a diagnosis of kidney cancer or bladder cancer in respective cohorts or censoring on death from any cause, end of registration with the general practice, or the end of study period (31st December 2017), which ever occurred first.

Covariates

All models were adjusted for the following covariates measured at cohort entry: age, body mass index (BMI, modelled as a continuous variables), year of cohort entry, duration of BPH (measured as time between date of BPH diagnosis and cohort entry), smoking status (current, former, or never), alcohol consumption (yes or no), type 2 diabetes mellitus, hypertension, urinary tract infection, cystitis, bladder stones, and kidney stones. Comorbidities were also extracted based on the Charlson's Comorbidities Index including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, dementia, diabetes, hemiplegia, liver disease, myocardial infarction, peripheral vascular disease, renal disease and rheumatological disease (21,22).

Statistical Analysis

We calculated the crude incidence rate and 95% confidence intervals based on Poisson distribution for 5ARi users. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for kidney or bladder cancer risk associated with 5ARi use compared to alpha-blocker use, adjusting for confounders mentioned previously. To investigate any duration-response relationship we calculated drug quantity and strength using the World Health Organisation defined daily doses (DDD) methodology (23). Using DDD we categorised drug use as less than 365 DDD, between 365-1095 DDD, and more than 1095 DDD as a time-varying variable. In addition, we modelled time since initiation as a time-varying variable categorised as 1 year or less, 1.1 to 3 years, and longer than 3 years. As a secondary analysis we used an alternative exposure definition whereby patients were censored on switching or adding on of the two study drugs, applying a one-year lag period.

Finally, as 5ARi and alpha-blockers are often prescribed together in clinical practice to effectively treat more severe BPH as secondary analyses we conducted analyses that allowed for the inclusion concomitant users in our cohort. For this analysis cohort entry date was considered the date of BPH diagnosis, with exclusion criteria outlined previously applied at cohort entry. A one-year lag period was applied, thus follow-up began one year post cohort entry. A time-varying exposure definition was used with each person-day of follow up classified hierarchically into mutually exclusive categories including: 5ARi use, alpha-blocker use and non-use. All exposures were lagged by one year, thus patients initiating 5ARi were considered unexposed to one year after their first prescription and considered exposed thereafter. The reference category was non-use.

We performed several sensitivity analyses. Firstly, given uncertainties surrounding cancer latency windows we varied the length of the lag period to 2 and 3 years. Secondly, as the alpha-blockers indoramin and prazosin more likely to be used for the treatment of hypertension we excluded this from our analysis to account for potential confounding by hypertension. Thirdly, to account for the competing risk due to death we applied competing risk analysis using the subdistribution model proposed by Fine and Gray (24). In addition, the primary analysis was repeated using multiple imputation for variables with missing values. An ordinal logistic regression model was used to impute variables with missing information (including smoking, alcohol use and BMI). Ten imputations were conducted, and results combined using Rubin's rules (25). Finally, the models were weighted using standardised mortality ratio weights (SMRW) using propensity scores (26). The propensity scores were estimated using logistic regression on the probability of receiving a 5ARi versus an alpha-blocker based on the previously mentioned covariates. Patients in the non-overlapping regions of the propensity score were trimmed and excluded from analysis.

All analyses were performed using STATA Release 16 (StataCorp, College Station, TX, USA).

Data Availability

The data analysed in this study are available from CPRD. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors upon reasonable request with the permission of CPRD.

Results

Table 1 presents baseline characteristics of 5ARi and alpha-blocker users for study cohorts. Exposure groups were similar in BMI, smoking status, alcohol use, and history of kidney and bladder stones. Users of 5ARi's were generally older with lower levels of hypertension compared to alpha-blocker users as expected with the clinical recommendations for drug use. History of myocardial infarction, peptic ulcer disease, and urinary tract infections was higher among users of 5ARi's in comparison to alpha-blocker users.

5-Alpha Reductase Inhibitors and Kidney Cancer

For the analysis of kidney cancer, we identified 5,008 and 35,076 new users of 5ARi's and alpha-blockers, respectively (Figure 1). During a median (IQR) duration of 6.4 (3.2-9.6) years of follow-up (excluding one-year lag) there were 23 incident events of kidney cancer among 5ARi users compared to 133 incident cases among alpha-blocker users (crude incidence rate: 70.5 vs 57.0 per 100,000 person years, respectively). Overall, compared to alpha-blocker use, we did not observe an association between 5ARi use and kidney cancer risk (adjusted HR: 1.26, 95%CI: 0.74-2.12; Table 2). No dose or duration response was observed in analysis of DDD's or time since initiation. Table 3 displays the results of secondary analyses censoring on switching or adding-on of the medications of interest. Overall, 44% (n=2,186) of 5ARi users at baseline switched or added-on an alpha-blocker and 30% (n=10,501) of alpha-blocker users at baseline switched or added-on a 5ARi. While estimates were attenuated to below the null, (adjusted HR: 0.77, 95%CI: 0.35-1.70, Table 3) there was no evidence of an association with wide CIs around the estimate and a low number of events (n=10). In addition, when comparing 5ARi use (5ARi use only and in combination with

alpha blockers) to non-use estimates were similar (adjusted HR: 1.17, 95%CI: 0.76-1.81) as shown in Supplementary Table S1.

Details of sensitivity analysis can be found in Supplementary Table S2. The estimates were attenuated towards the null when varying lag periods to 2 years (HR: 1.15, 95%CI: 0.65-2.04) and 3 years (HR: 1.15, 95%CI: 0.60-2.18; Figure 2A). Similarly, estimates were attenuated when using multiple imputation (HR: 1.16, 95%CI: 0.74-1.82) and using standard mortality ratio weights based upon the propensity score (weighted HR: 1.08, 95% CI: 0.61-1.91; Figure 2A). Baseline characteristics with absolute standardised differences before and after weighting are shown in Supplementary Table S3. The estimate was consistent with the exclusion of the alpha-blockers less likely to be solely prescribed in BPH treatment and competing risk of death analysis (Figure 2A).

5-Alpha Reductase Inhibitors and Bladder Cancer

For bladder cancer analysis, we identified 4,993 and 35,010 new users of 5ARi and alpha-blockers, respectively (Figure 1). During a median (IQR) duration of 6.3 (3.2-9.5) years of follow-up (excluding one-year lag) there were 57 incident events of bladder cancer among 5ARi users compared to 402 incident cases among alpha-blocker users (crude incidence rate: 175.6 vs 173.4 per 100,000 person years, respectively). There was no association between 5ARi use and bladder cancer in comparison to alpha-blocker use (adjusted HR: 0.89 95%CI: 0.64-1.23; Table 2). Additionally, analysis by DDD category and time since initiation revealed no evidence of a dose response relation of 5ARi use with bladder cancer risk (Table 2). In the secondary analysis censoring on switching or add-on of medication the estimate was attenuated (Table 3). Overall, 44% (n=2,182) of 5ARi users at baseline switched or added-on an alpha-blocker and 30% (n=10,482) of alpha-blocker users at baseline switched

or added-on a 5ARi. In addition, results for exposure to 5ARi's compared to non-use were null (adjusted HR: 0.96, 95%CI: 0.73-1.26; Supplementary Table S1).

The sensitivity analysis was consistent when varying lag periods to 2 years and 3 years, excluding alpha-blockers less likely to be prescribed in BPH treatment, using competing risk of death analysis, using multiple imputation, and using standard mortality ratio weights as a propensity score analysis (Figure 2B; Supplementary Table S2). Supplementary Table S4 presents baseline characteristics with absolute standardised differences before and after weighting.

Discussion

In this large population-based study we investigated whether 5ARi use was associated with a reduction in the risk of kidney or bladder cancer when compared to alpha-blocker use. We found no association between the use of 5ARi in men with BPH and risk of kidney or bladder cancer, with no evidence of a dose-response relation.

Studies investigating the association of 5ARi use with bladder cancer initially reported a reduced risk of bladder cancer with 5ARi use. An early study by Morales *et al* found a 37% reduced risk of bladder cancer with the use of finasteride (n=65) in a US trial population using time-to-event analysis (HR: 0.63, 95% CI: 0.49-0.82) (11). Another study conducted in the US, reported a 36% reduced risk of bladder cancer (HR: 0.64, 95% CI: 0.51-0.80) based on 86 bladder cancer events among 5ARi users (12). Notably, both studies likely suffered from immortal time bias, likely explaining the risk reductions observed. This bias is introduced when there is a period of follow-up time in which the outcome cannot occur due to the exposure definition resulting in misclassification of the immortal time (27). The studies also had other limitations including the use of a non-user comparator (11,12), inclusion of prevalent users (11), lack of inclusion of a lag period (12), and potential residual confounding by patient characteristics such as smoking and BMI (11,12). While we observed non-significant reductions in HR's overall and in sensitivity analyses, we found no evidence of duration response. Thus, our results are in line with an additional cohort study conducted in men with prostatic symptoms that concluded there was no evidence of an association although this study was limited by low number of events (n=9) (14).

Evidence regarding kidney cancer risk with 5ARi's is very limited. Similar to our findings, a cohort study of clinical trial data with a maximum follow-up of 15 years observed no

association between finasteride use and kidney cancer risk (n= 52, HR: 1.12, 95% CI: 0.83-1.5) when comparing to non-use (15). However, this study was limited by potential exposure misclassification due to self-reported use of finasteride and lack of a lag period to account for the long latency of cancer (15).

The biological rationale for the relationship between 5ARi's and urological cancers stem from observed sex discrepancies in cancer incidence and suggest a role of the male hormonal pathway in cancer initiation (3,4,28). In-vitro studies suggest modulation of DHT and AR activity in both kidney and bladder cancer are closely linked with cancer progression (6-9,29). One study found that genomic alterations of the 5-alpha reductase enzymes, the target for 5ARi's, was found in almost one third of bladder cancer cases (10). Furthermore, addition of finasteride to bladder cancer cells suppressed cell growth (10). Thus, 5ARi's may influence cancer risk via action on the 5-alpha reductase enzymes and the reduction of circulating levels of the potent male sex hormone DHT (2). In kidney cancer the epigenetic regulation of the AR, via its co-regulator lysine-specific histone demethylase 1, was linked with greater kidney cancer growth (9). The promotion of the AR pathway via other mechanism has also been highlighted to promote cancer initiation in kidney cancer (30). However, these proposed mechanisms for reduced cancer incidence with 5ARi use in kidney and bladder cancer are not reflected in this large population study.

This study has several strengths. It was a large retrospective cohort study utilising data from the UK CPRD with a long follow-up to investigate the long latency of cancer. This allowed collection of information on important confounders including BMI, smoking, and alcohol use. In addition, we compared 5ARi's to alpha-blockers using a new user active comparator

239 design excluding prevalent users and reducing confounding by indication by accounting for
240 the severity of BPH requiring treatment.

241 However, this study also had some limitations. Low number of events in our cohort limited
242 our statistical power to detect a marginal effect especially in kidney cancer analysis. Our
243 analysis was in line with another study with a greater number of events of kidney cancer
244 (n=52) (15). We were unable to stratify by cancer stage, location, or histological sub-type as
245 this information was unavailable in the CPRD. Further studies with greater number of events
246 using a new-user active comparator approach would be required to confirm our null findings
247 and by sub-type of cancer. Misclassification of the outcome was possible however cancer
248 diagnoses for kidney and bladder cancer have been shown to be well recorded in the CPRD
249 (19). The UK CPRD allowed consideration of many potential confounders however residual
250 confounding from occupation remains a possibility. Thirdly, the CPRD captures prescription
251 records from general practice therefore misclassification of the exposure is possible due to
252 non-adherence to treatment or missed prescriptions from specialists. A previous study of
253 BPH patients in CPRD indicated that adherence to 5ARi's and alpha-blockers is relatively low
254 (32.3% and 44%, respectively) (31). However, dose response relations were also evaluated,
255 with noncompliance less of a concern for those using multiple prescriptions. In addition, our
256 base cohort was identified based on a diagnosis of BPH prior to treatment. The
257 misclassification of BPH in our base cohort may be possible as diagnoses are not confirmed
258 by imaging but rather by medical history and physical examination, unless concerns about
259 complications exist (1). Lastly, increased surveillance of patients by clinicians close to
260 treatment initiation may lead to increased detection of kidney or bladder cancer,
261 particularly as bladder-related symptoms are common between both BPH and bladder
262 cancer. We addressed this by using an active comparator and introducing a 1-year lag period

263 which was varied in sensitivity analysis. Reassuringly, results for bladder cancer remained
264 consistent in lagged analysis, while estimates were attenuated towards the null for kidney
265 cancer on the application of a 2-year lag. This attenuation in our lag analysis could indicate
266 the need to consider a longer lag period for kidney cancer.

267 In conclusion, this population-based study found no reduction in the risk of kidney or
268 bladder cancer with the use of 5ARi's in men with BPH. This does not support previous
269 observations of a reduced risk of bladder cancer. Given the low numbers of kidney cancer
270 events observed in the current study further studies would be warranted to confirm the
271 findings.

References

1. 2010 03/11/2020. Lower urinary tract symptoms in men: management. National Institute for Health and Care Excellence <https://www.nice.org.uk/guidance/cg97>. Accessed 2020 03/11/2020.
2. Clark RV, Hermann DJ, Cunningham GR, Wilson TH, Morrill BB, Hobbs S. Marked Suppression of Dihydrotestosterone in Men with Benign Prostatic Hyperplasia by Dutasteride, a Dual 5α-Reductase Inhibitor. The Journal of Clinical Endocrinology & Metabolism **2004**;89(5):2179-84 doi 10.1210/jc.2003-030330.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians **2018**;68(6):394-424 doi 10.3322/caac.21492.
4. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M*, et al.* Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International Journal of Cancer **2019**;144(8):1941-53 doi 10.1002/ijc.31937.
5. Hu C, Fang D, Xu H, Wang Q, Xia H. The androgen receptor expression and association with patient's survival in different cancers. Genomics **2020**;112(2):1926-40 doi https://doi.org/10.1016/j.ygeno.2019.11.005.
6. Kawahara T, Shareef HK, Aljarah AK, Ide H, Li Y, Kashiwagi E*, et al.* ELK1 is up-regulated by androgen in bladder cancer cells and promotes tumor progression. Oncotarget **2015**;6(30):29860-76 doi 10.18632/oncotarget.5007.
7. Inoue S, Ide H, Mizushima T, Jiang G, Netto GJ, Gotoh M*, et al.* Nuclear Factor-κB Promotes Urothelial Tumorigenesis and Cancer Progression via Cooperation with Androgen Receptor Signaling. Molecular Cancer Therapeutics **2018**;17(6):1303-14 doi 10.1158/1535-7163.Mct-17-0786.
8. Miyamoto H, Yang Z, Chen Y-T, Ishiguro H, Uemura H, Kubota Y*, et al.* Promotion of Bladder Cancer Development and Progression by Androgen Receptor Signals. JNCI: Journal of the National Cancer Institute **2007**;99(7):558-68 doi 10.1093/jnci/djk113.
9. Lee KH, Kim BC, Jeong SH, Jeong CW, Ku JH, Kwak C*, et al.* Histone Demethylase LSD1 Regulates Kidney Cancer Progression by Modulating Androgen Receptor Activity. Int J Mol Sci **2020**;21(17) doi 10.3390/ijms21176089.
10. Chen CC, Huang CP, Tsai YT, Hseih TF, Shyr CR. The Genomic Alterations of 5α-Reductases and Their Inhibitor Finasteride's Effect in Bladder Cancer. Anticancer Res **2017**;37(12):6893-8 doi 10.21873/anticanres.12152.
11. Morales EE, Grill S, Svatek RS, Kaushik D, Thompson IM, Jr., Ankerst DP*, et al.* Finasteride Reduces Risk of Bladder Cancer in a Large Prospective Screening Study. Eur Urol **2016**;69(3):407-10 doi 10.1016/j.eururo.2015.08.029.
12. Zhu D, Srivastava A, Agalliu I, Fram E, Kovac EZ, Aboumohamed A*, et al.* Finasteride Use and Risk of Bladder Cancer in a Multiethnic Population. J Urol **2021**;206(1):15-21 doi https://doi.org/10.1097/JU.0000000000001694.
13. Wang CS, Li CC, Juan YS, Wu WJ, Lee HY. 5α-reductase inhibitors impact prognosis of urothelial carcinoma. BMC Cancer **2020**;20(1):872 doi 10.1186/s12885-020-07373-4.
14. Sathianathen NJ, Fan Y, Jarosek SL, Lawrentschuk NL, Konety BR. Finasteride does not prevent bladder cancer: A secondary analysis of the Medical Therapy for Prostatic Symptoms Study. Urol Oncol **2018**;36(7):338.e13-.e17 doi 10.1016/j.urolonc.2018.03.020.
15. Kabra A, Gelfond J, Liss MA. Hormonal manipulation with finasteride or oral contraception does not influence incidence of renal cell carcinoma. Eur J Cancer Prev **2018**;27(5):449-52 doi 10.1097/cej.0000000000000345.
16. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Current epidemiology reports **2015**;2(4):221-8 doi 10.1007/s40471-015-0053-5.

17. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T*, et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol **2015**;44(3):827-36 doi 10.1093/ije/dyv098.
18. Jick SS, Kaye JA, Vasilakis-Scaramozza C, Rodríguez LAG, Ruigómez A, Meier CR*, et al.* Validity of the General Practice Research Database. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy **2003**;23(5):686-9 doi https://doi.org/10.1592/phco.23.5.686.32205.
19. Boggon R, van Staa TP, Chapman M, Gallagher AM, Hammad TA, Richards MA. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. Pharmacoepidemiology and Drug Safety **2013**;22(2):168-75 doi https://doi.org/10.1002/pds.3374.
20. Sendor R, Stürmer T. Core Concepts in Pharmacoepidemiology: Confounding by Indication and the Role of Active Comparators. Pharmacoepidemiology and Drug Safety **2022**;n/a(n/a) doi https://doi.org/10.1002/pds.5407.
21. Payne RA, Mendonca SC, Elliott MN, Saunders CL, Edwards DA, Marshall M*, et al.* Development and validation of the Cambridge Multimorbidity Score. Canadian Medical Association Journal **2020**;192(5):E107-E14 doi 10.1503/cmaj.190757.
22. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Family Practice **2010**;11(1):1 doi 10.1186/1471-2296-11-1.
23. Nahler G. Dictionary of Pharmaceutical Medicine. Vienna: Springer Vienna; 2009.
24. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association **1999**;94(446):496-509 doi 10.1080/01621459.1999.10474144.
25. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG*, et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj **2009**;338:b2393 doi 10.1136/bmj.b2393.
26. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ **2019**;367:l5657 doi 10.1136/bmj.l5657.
27. Suissa S. Immortal Time Bias in Pharmacoepidemiology. American Journal of Epidemiology **2007**;167(4):492-9 doi 10.1093/aje/kwm324.
28. Zhu Y, Shao X, Wang X, Liu L, Liang H. Sex disparities in cancer. Cancer Letters **2019**;466:35-8 doi https://doi.org/10.1016/j.canlet.2019.08.017.
29. Hata S, Ise K, Azmahani A, Konosu-Fukaya S, McNamara KM, Fujishima F*, et al.* Expression of AR, 5αR1 and 5αR2 in bladder urothelial carcinoma and relationship to clinicopathological factors. Life sciences **2017**;190:15-20 doi 10.1016/j.lfs.2017.09.029.
30. Wang Z, Song Y, Ye M, Dai X, Zhu X, Wei W. The diverse roles of SPOP in prostate cancer and kidney cancer. Nature Reviews Urology **2020**;17(6):339-50 doi 10.1038/s41585-020-0314-z.
31. Ayele HT, Reynier P, Azoulay L, Platt RW, Cabaussel J, Benayoun S*, et al.* Trends in the pharmacological treatment of benign prostatic hyperplasia in the UK from 1998 to 2016: a population-based cohort study. World Journal of Urology **2021**;39(6):2018-28 doi 10.1007/s00345-020-03429-z.

Table 1. Baseline characteristics

Characteristics	Kidney Cancer Cohort		Bladder Cancer Cohort	
	5ARi Users N= 5,008	Alpha-Blocker Users N= 35,076	5ARi Users N= 4,993	Alpha-Blocker Users N= 35,010
Age, years (mean, SD)	71.3 (9.6)	68.1 (9.8)	71.3 (9.6)	68.1 (9.8)
Year of Cohort Entry, n (%)				
1998-2001	1,090 (21.8)	6,699 (19.1)	1,088 (21.8)	6,689 (19.1)
2002-2005	1,716 (34.3)	11,771 (33.6)	1,711 (34.3)	11,758 (33.6)
2006-2009	1,814 (36.2)	12,418 (35.4)	1,809 (36.2)	12,386 (35.4)
2010-2014	388 (7.8)	4,188 (11.9)	385 (7.7)	4,177 (11.9)
Duration of BPH, months (mean, SD)	12.9 (27.7)	14.6 (30.3)	12.8 (27.7)	14.6 (30.3)
Body Mass Index, n (%)				
<18.5 kg/m^2	35 (0.7)	208 (0.6)	35 (0.7)	206 (0.6)
18.5-24.9 kg/m^2	1,314 (26.2)	8,943 (25.5)	1,305 (26.1)	8,927 (25.5)
25-30 kg/m^2	1,973 (39.4)	13,404 (38.2)	1,968 (39.4)	13,375 (38.2)
≥30 kg/m^2	749 (15.0)	5,942 (16.9)	749 (15.0)	5,941 (17.0)
Unknown	937 (18.7)	6,579 (18.8)	936 (18.8)	6,561 (18.7)
Smoking Status, n (%)				
Current	594 (11.9)	4,476 (12.8)	592 (11.9)	4,465 (12.8)
Past	1,835 (36.6)	12,434 (35.5)	1,828 (36.6)	12,407 (35.4)
Never	2,106 (42.1)	14,830 (42.3)	2,102 (42.1)	14,812 (42.3)
Unknown	473 (9.4)	3,336 (9.5)	471 (9.4)	3,326 (9.5)
Alcohol Status, n (%)				
Yes	3,445 (68.8)	23,806 (67.9)	3,436 (68.8)	23,763 (67.9)
No	477 (9.5)	3,254 (9.3)	475 (9.5)	3,256 (9.3)
Unknown	1,086 (21.7)	8,016 (22.9)	1,082 (21.7)	7,991 (22.8)
Disease History, n (%)				
Hypertension	2,950 (58.9)	22,740 (64.8)	2,942 (58.9)	22,690 (64.8)
Renal Disease	334 (6.7)	1,875 (5.4)	331 (6.6)	1,866 (5.3)
Diabetes	577 (11.5)	3,690 (10.5)	577 (11.6)	3,686 (10.5)
Myocardial Infarction	522 (10.4)	2485 (7.1)	520 (10.4)	2481 (7.1)
Peptic Ulcer Disease	374 (7.5)	2362 (6.7)	373 (7.5)	2356 (6.7)
Urinary Tract Infections	792 (15.8)	4,259 (12.1)	789 (15.8)	4,240 (12.1)
Kidney Stones	316 (6.3)	2,052 (5.9)	316 (6.3)	2,053 (5.9)
Bladder Stones	30 (0.6)	115 (0.3)	30 (0.6)	115 (0.3)

Table 2. Crude and adjusted hazard ratio for the association between 5ARi's and kidney cancer and bladder cancer compared to alpha-blocker

Subgroup	Events	Person Years	Incidence Rate [a] (95% CI)	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
Kidney Cancer					
Alpha-Blockers	133	233297	57.01 (48.10-67.57)	1.00 (ref.)	1.00 (ref)
5ARi	23	32636	70.47 (46.83-106.05)	1.24 (0.80-1.93)	1.26 (0.74-2.12)
Defined Daily Dose Categories					
<365	7	11494	60.90 (29.03-127.74)	1.08 (0.50-2.31)	0.69 (0.22-2.20)
364-1095	7	9437	74.17 (35.36-155.59)	1.35 (0.63-2.91)	1.52 (0.65-3.53)
≥1095	9	11705	76.89 (40.01-147.78)	1.30 (0.66-2.57)	1.53 (0.73-3.20)
Time Since 5ARi Initiation					
<1 year	S	S	83.488 (31.33-222.45)	2.01 (0.66-6.11)	2.72 (0.70-10.54)
1-2.9 years	S	S	35.985 (11.61-111.57)	0.61 (0.19-1.98)	0.69 (0.21-2.28)
≥3 years	16	19508	82.015 (50.24-133.87)	1.37 (0.80-2.34)	1.36 (0.71-2.61)
Bladder Cancer					
Alpha-Blockers	402	231882	173.36 (157.22-191.17)	1.00 (ref.)	1.00 (ref)
5ARi	57	32469	175.55 (135.41-227.58)	1.01 (0.76-1.34)	0.89 (0.64-1.23)
Defined Daily Dose Categories					
<365	11	11424	96.29 (53.32-173.87)	0.55 (0.30-0.99)	0.61 (0.31-1.18)
364-1095	24	9400	2555.31 (171.13-380.91)	1.47 (0.97-2.23)	1.37 (0.85-2.19)
≥1095	22	11645	188.92 (124.39-286.91)	1.11 (0.72-1.71)	0.76 (0.44-1.31)
Time Since 5ARi Initiation					
<1 year	12	4772	251.47 (142.81-442.80)	1.24 (0.67-2.30)	1.35 (0.70-2.61)
1-2.9 years	13	8293	156.77 (91.03-269.98)	0.96 (0.54-1.72)	0.67 (0.32-1.39)
≥3 years	32	19404	164.90 (116.62-233.19)	0.96 (0.67-1.39)	0.85 (0.55-1.32)

Abbreviations: HR, Hazard Ratio, CI, confidence interval, 5ARi, 5-alpha reductase inhibitor

[a] Crude incidence rate per 100,000 person years

[b] Adjusted for Age, Year of Cohort Entry, Duration of BPH, Smoking Status, Alcohol Status, Body Mass Index, Hypertension, cerebrovascular disease, chronic pulmonary disease, congestive heart disease, dementia, diabetes, hemiplegia, liver disease, myocardial infarction, peripheral vascular disease, renal disease, rheumatological disease, urinary tract infections, cystitis, bladder stones and kidney stones.

S Number of events <5 and corresponding person years were suppressed per CPRD confidentiality policy

Table 3. Crude and adjusted hazard ratios for the association between 5ARi's and kidney and bladder cancer compared with alpha-blockers, censoring on treatment switching

Subgroup	Events	Person Years	Incidence Rate (95% CI) [a]	Crude HR (95% CI)	Adjusted HR (95% CI) [b]
Kidney Cancer					
Alpha-Blockers	104	187119	45.90 (24.70-85.31)	1.00 (ref.)	1.00 (ref)
5ARi	10	21786	55.58 (45.86-67.36)	0.83 (0.44-1.59)	0.77 (0.35-1.70)
Bladder Cancer					
Alpha-Blockers	328	186154	176.20 (158.13-196.34)	1.00 (ref.)	1.00 (ref)
5ARi	34	21686	156.78 (112.03-219.42)	0.88 (0.62-1.25)	0.75 (0.49-1.14)

Abbreviations: HR, Hazard Ratio, CI, confidence interval, 5ARi, 5-alpha reductase inhibitor

[a] Crude incidence rate per 100,000 person years

[b] Adjusted for Age, Year of Cohort Entry, Duration of BPH, Smoking Status, Alcohol Status, Body Mass Index, Hypertension, cerebrovascular disease, chronic pulmonary disease, congestive heart disease, dementia, diabetes, hemiplegia, liver disease, myocardial infarction, peripheral vascular disease, renal disease, rheumatological disease, urinary tract infections, cystitis, bladder stones and kidney stones

Figure Legends

Figure 1. Flowchart outlining the construction of the kidney and bladder cancer cohorts of new users of 5-alpha reductase inhibitors and alpha blockers

Figure 2. Forest plots of primary and sensitivity analysis with adjusted hazard ratios and 95% confidence intervals for the association between use of 5-alpha reductase inhibitors and (**A**) kidney cancer and (**B**) bladder cancer

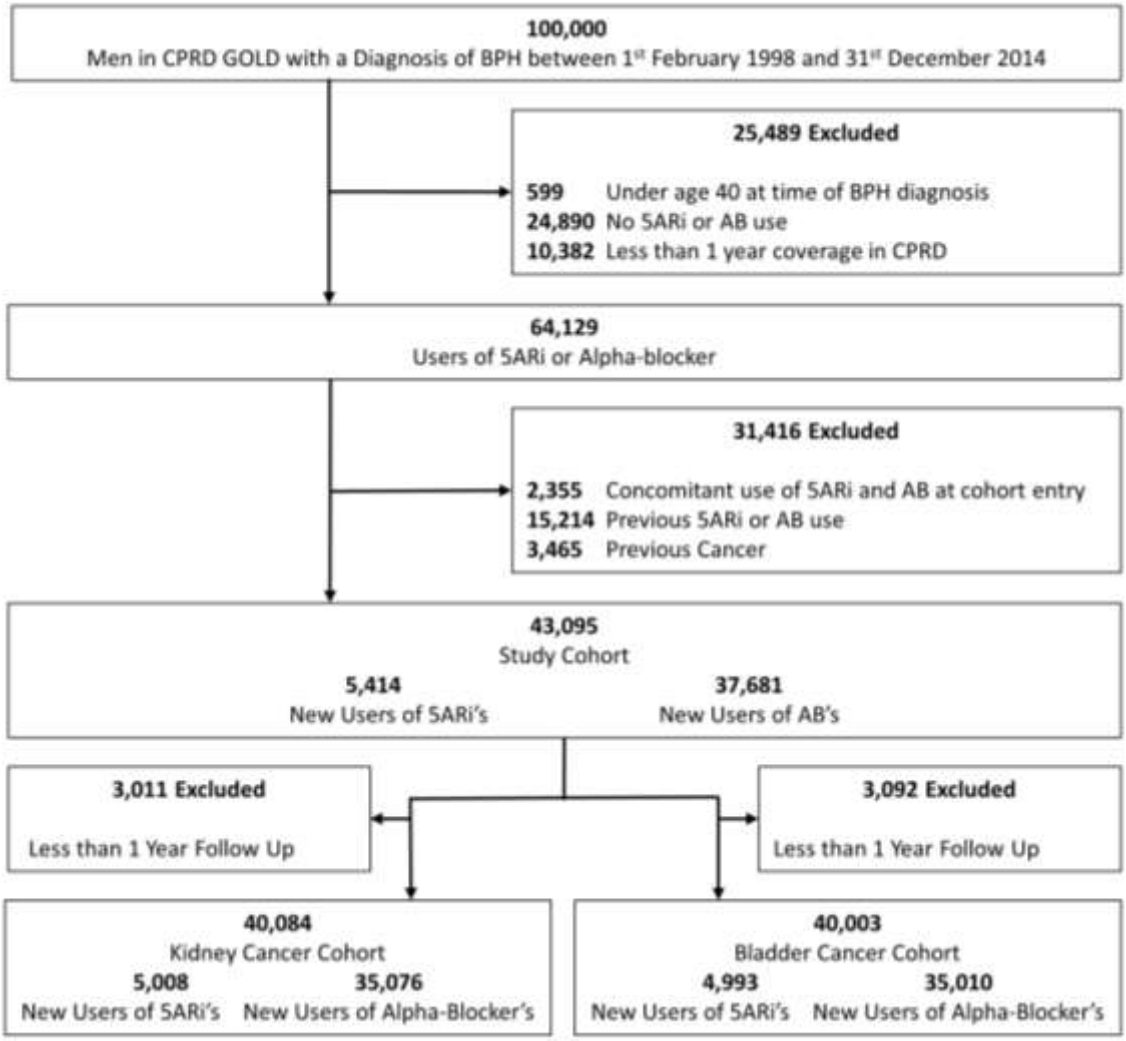

Figure 1. Flowchart outlining the construction of the kidney and bladder cancer cohorts of new users of 5-alpha reductase inhibitors and alpha blockers

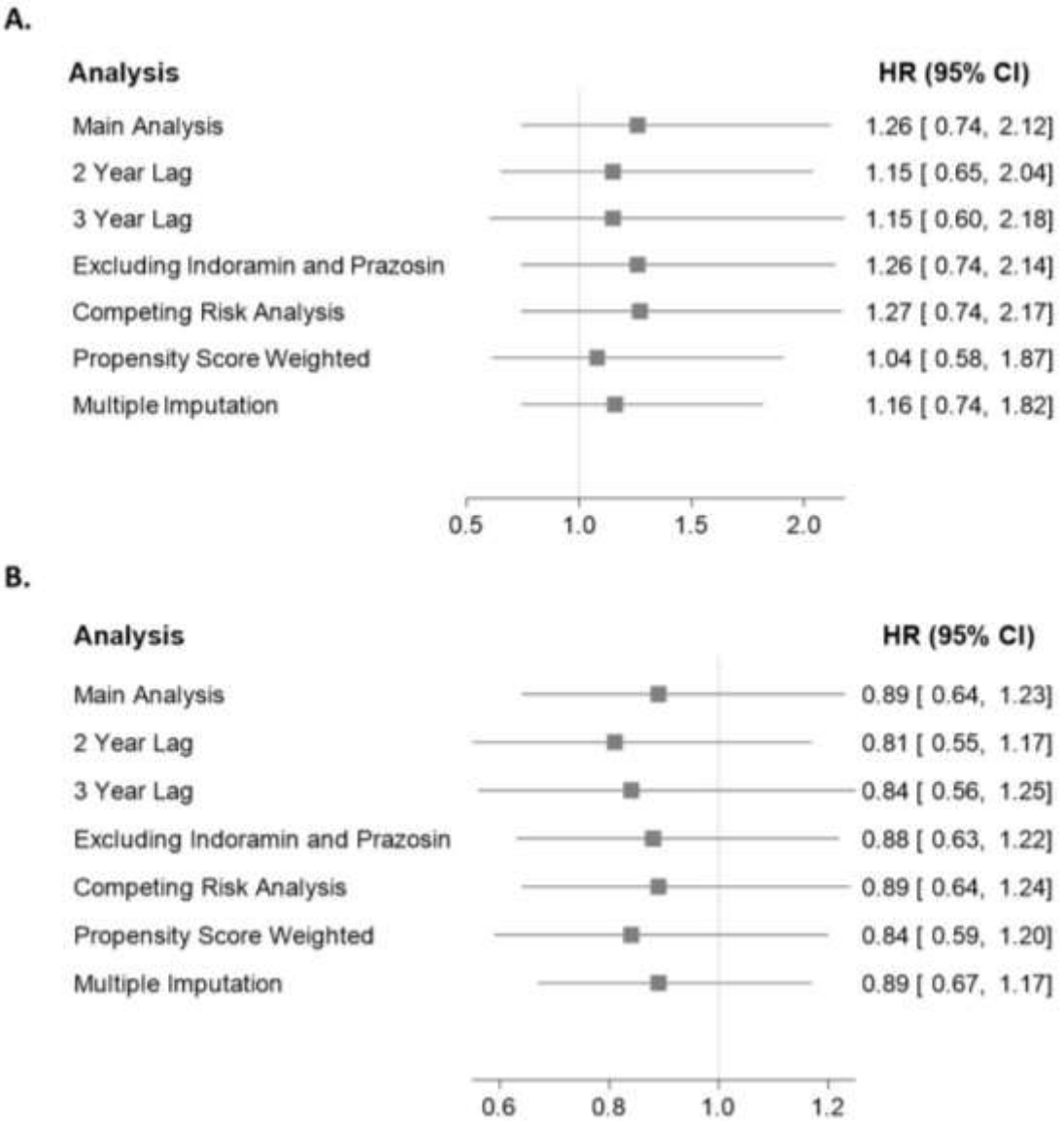

Figure 2. Forest plots of primary and sensitivity analysis with adjusted hazard ratios and 95% confidence intervals for the association between use of 5-alpha reductase inhibitors and (**A**) kidney cancer and (**B**) bladder cancer