5α-Reductase Inhibitors and the Risk of Cancer-Related Mortality in Men With Prostate Cancer

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IMPORTANCE 5α-Reductase inhibitors (5-ARIs) are widely used in the treatment of benign prostatic hyperplasia. However, randomized clinical trials have raised concerns that their use may be associated with an increased risk of high-grade prostate cancer tumors that would ultimately lead to worse prostate cancer outcomes. To date, few observational studies have addressed this important safety concern.

OBJECTIVE To determine whether the use of 5-ARIs before prostate cancer diagnosis is associated with an increased risk of cancer-specific and all-cause mortality in men with a new diagnosis of prostate cancer in the real-world setting.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted in a cohort of 13 892 men with a new diagnosis of prostate cancer between January 1, 1999, and December 31, 2009, who were followed up until October 1, 2012. Patients were individually linked across 4 databases from the United Kingdom: National Cancer Data Repository, Clinical Practice Research Datalink, Hospital Episodes Statistics database, and Office for National Statistics database.

MAIN OUTCOMES AND MEASURES Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% CIs of prostate cancer–specific and all-cause mortality associated with prediagnostic use of 5-ARIs. For each outcome, 2 models were constructed, one adjusted for predefined covariates (conventional model) and another adjusted for high-dimensional propensity score (HD-PS) deciles.

RESULTS During a mean (SD) of 4.5 (3.1) years, 5001 deaths occurred, including 2429 from prostate cancer (crude incidence rate of 3.86 per 100 person-years [95% CI, 3.71-4.02]). In the conventional model, use of 5-ARIs before prostate cancer diagnosis was not associated with an increased risk of prostate cancer–specific mortality (crude incidence rates, 3.76 [95% CI, 3.04-4.59] [use] vs 3.87 [95% CI, 3.71-4.03] [nonuse] per 100 person-years; adjusted hazard ratio [aHR], 0.86 [95% CI, 0.69-1.06]) and all-cause mortality (crude incidence rates, 8.42 [95% CI, 7.32-9.64] [use] vs 7.93 [95% CI, 7.71-8.16] [nonuse] per 100 person-years; aHR, 0.87; 95% CI, 0.75-1.00). Similar results were observed with the HD-PS adjusted model (prostate cancer–specific mortality: aHR, 0.90 [95% CI, 0.73-1.13]; and all-cause mortality: aHR, 0.92 [95% CI, 0.80-1.07]).

CONCLUSIONS AND RELEVANCE The use of 5-ARIs was not associated with an increased risk of prostate cancer–specific and all-cause mortality in men with a new diagnosis of prostate cancer. While these results provide reassurance, additional studies are needed to replicate these findings.

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In men with benign prostatic hyperplasia (BPH), 5α-reductase inhibitors (5-ARIs), such as finasteride and dutasteride, are effective in the treatment of lower urinary tract symptoms.[1] However, their role in prostate cancer chemoprevention remains controversial. Two large randomized clinical trials, the Prostate Cancer Preventive Trial (PCPT)[2] and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE),[3] observed 25% and 23% risk reductions, respectively, in prostate cancer incidence with the use of 5-ARIs.[2,3] However, patients randomized to 5-ARIs had an unexpected increased risk of high-grade tumors compared with placebo.[2,3] The clinical significance of this paradoxical finding has been the subject of debate, with several proposing that they are the result of a detection bias.[4-7] This is because 5-ARIs decrease prostate volume and improve prostate-specific antigen and digital rectal examination sensitivities, all of which would increase the probability of detecting high-grade tumors at biopsy.[4,6] However, owing to continued concerns, the US Food and Drug Administration warned against the use of 5-ARIs for prostate cancer chemoprevention.[8]

It can be hypothesized that if 5-ARIs increase the risk of high-grade tumors, they should in turn increase the risk of prostate cancer outcomes, such as recurrence and mortality. To date, however, there are few and conflicting studies assessing the effects of 5-ARIs on such prostate cancer outcomes.[9-11] Recently, a post hoc analysis of the PCPT trial revealed that finasteride, compared with placebo, was not associated with an increased risk of death from any cause among men diagnosed as having prostate cancer.[12] While this study provides some reassurance, it was conducted within a selected and highly screened population that may not reflect clinical practice, and the null association with all-cause mortality does not rule out an association with prostate cancer–specific mortality,[13] the primary outcome of interest.

Thus, given the prevalent use of 5-ARIs in men with BPH and continued concerns regarding their safety on prostate cancer incidence, we conducted a large population-based study to determine whether the use of these drugs is associated with an increased risk of prostate cancer–specific mortality in men with newly diagnosed prostate cancer. A secondary objective was to assess this relationship with all-cause mortality.

At a Glance

- 5α-Reductase inhibitors (5-ARIs) are used in the treatment of benign prostate hypertrophy; however, there are some concerns that use raises the risk of high-grade prostate cancers.
- A retrospective study was performed on a cohort of 13 892 men with prostate cancer followed up over a 12-year period (mean follow-up of 4.5 years).
- The use of 5-ARIs prior to prostate cancer diagnosis was not associated with an increased risk of prostate cancer–specific and all-cause mortality.

Methods

Data Sources

This study was conducted by linking 4 large electronic databases from the United Kingdom (UK): the National Cancer Data Repository (NCDR), the Clinical Practice Research Datalink (CPRD), the Hospital Episode Statistics (HES) database, and the Office for National Statistics (ONS) database.

The NCDR contains tumor information, including site of primary growth (coded using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*]) and tumor characteristics. The CPRD contains data on more than 12 million individuals enrolled in over 650 general practices and has been shown to be representative of the UK population.[14] Read codes are used to enter medical diagnoses and procedures,[15] and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used for recording prescriptions. The recorded information on diagnoses and drug exposures in the CPRD are regularly audited, have been validated, and have been shown to be of high quality.[16-20]

Since 1997, the HES database records details of all hospital encounters, including admission dates, primary and secondary diagnoses (coded using the *ICD-10* classification), and procedures (coded using the *Classification of Interventions and Procedures, Fourth Revision*[21]) in English National Health Services hospitals. Finally, the ONS contains the electronic death certificates of all citizens living in the UK; thus, it was necessary to establish the date and the underlying cause of death (based on *ICD-10* codes) of all patients who died during follow-up.

The study protocol (#13_153) was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study Population

In our retrospective cohort study, the NCDR was first used to identify all patients newly diagnosed as having prostate cancer (*ICD-10* code C61) between January 1, 1999, and December 31, 2009, which were then linked to the CPRD, HES, and ONS databases. Patients were required to have at least 2 years of medical history in the CPRD before the prostate cancer diagnosis (ie, cohort entry). All patients were followed up until death, end of registration with the general practice, or end of study period (October 1, 2012), whichever came first.

Exposure to 5α-Reductase Inhibitors

We identified all patients who were prescribed finasteride (5 mg) and dutasteride (0.5 mg) at any time before cohort entry, excluding prescriptions initiated in the 12 months immediately before cohort entry. This lag period was necessary to minimize reverse causality, a situation where some patients may have been prescribed 5-ARIs for BPH to treat initial symptoms of yet undiagnosed prostate cancer, and to account for a latency time window, given that short exposure durations are unlikely to affect prostate cancer prognosis.

Exposure to 5-ARIs was defined as prediagnostic use and cumulative duration of use. Prediagnostic use, which was considered the primary exposure definition, was defined as receiving at least 1 prescription of a 5-ARI at any time up until

the 12 months immediately before cohort entry. In the second approach, it was of interest to determine whether there was a duration-response relationship with the mortality outcomes (prostate cancer–specific and all-cause mortality). Thus, for this analysis, cumulative duration of use was calculated by summing the durations of all 5-ARI prescriptions received among patients deemed to be prediagnostic users. This variable was then categorized in tertiles in the models. The reference category for all analyses was nonexposure to 5-ARIs at any time up until the 12 months before cohort entry.

Potential Confounders

The models were adjusted for the following variables measured at cohort entry: age; calendar year of diagnosis; ethnicity; excessive alcohol use (based on diagnoses for alcohol-related disorders, such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure); smoking status; body mass index (BMI); Charlson Comorbidity Index[22] adapted for use in the CPRD[23]; and ever-use of aspirin, other nonsteroidal anti-inflammatory drugs, statins, and α-blockers (all measured at any time up until the 12 months before cohort entry). Variables with missing information, such as race/ethnicity, smoking, and BMI, were coded with an "unknown" category.

Prostate cancer–related variables such as Gleason score, prostate-specific antigen serum level (last value before diagnosis), and presence of distant metastases at diagnosis were documented but not included as covariates because these variables are on the causal pathway between exposure (prediagnostic use of 5-ARIs) and outcome (prostate cancer–specific mortality).[24] Tumor stage was not documented because it was missing for approximately 90% of the cohort.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the cohort and characteristics stratified by prediagnostic use and nonuse of 5-ARIs. Crude incidence rates, with 95% CIs based on the Poisson distribution, were calculated by dividing the number of patients with prostate cancer–specific (underlying cause of death, *ICD-10* code C61) and all-cause mortality over the person-time at risk.

Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% CIs of prostate cancer–specific and all-cause mortality associated with prediagnostic use and cumulative duration of use of 5-ARIs. For the latter, linear trend was assessed by considering the tertile categories as a continuous variable in the models. All models were adjusted for the potential confounders listed in the previous subsection. Schoenfeld residuals were examined for all the covariates, and departures from the proportional hazards assumption were observed for age and calendar year of diagnosis; thus, interaction terms between those covariates and the logarithmic of time were introduced in the models.

To address potential residual confounding, we conducted a high-dimensional propensity score (HD-PS) analysis, which is based on an algorithm that empirically identifies covariates on their prevalence and potential for confounding.[25] Using multivariate logistic regression, we estimated a propensity score for each patient as the predicted probability of exposure conditional on all empirical and selected predefined covariates measured before cohort entry. The empirical covariates were estimated from 3 data dimensions: general practice–related variables (such as diagnoses, laboratory tests, and immunizations), drug prescriptions, and hospitalizations. The predefined covariates included age; year of diagnosis; race/ethnicity; excessive alcohol use; smoking status; BMI; Charlson Comorbidity Index; and ever-use of aspirin, other nonsteroidal anti-inflammatory drugs, statins, and α-blockers. After verifying overlap of the propensity score distributions between the exposure groups, the final Cox proportional hazards model was adjusted for propensity score decile categories (additional information is available in the eAppendix in the Supplement).

In an exploratory analysis, we constructed Kaplan-Meier curves of prostate cancer–specific mortality associated with prediagnostic use of 5-ARIs stratified by the presence of low-grade cancers (Gleason score, 2-6) vs high-grade cancers (Gleason score, 7-10). This analysis was restricted to patients with available Gleason scores as documented in the NCDR (n = 7074).

Sensitivity Analyses

We conducted 3 sensitivity analyses to assess the robustness of our results. First, given uncertainties related to the choice of the 12-month exposure lag period before cohort entry, we conducted a sensitivity analysis by varying the length of that time window to 0, 6, and 24 months. In a second sensitivity analysis, we assessed the impact of exposure misclassification that could have occurred if some patients were prescribed 5-ARIs prior to their registration in their current general practice. For this analysis, we restricted the cohort to patients initially registered in the CPRD in or before 1992, the year the first 5-ARI (finasteride) was licensed in the UK. Finally, for prostate cancer–specific mortality, we conducted a sensitivity analysis to account for competing risks due to death from other causes (mainly cardiovascular) using the subdistribution hazards model proposed by Fine and Gray.[26] All statistical analyses were 2-tailed tests based on an α level of .05 and were performed with SAS version 9.3 statistical software (SAS Institute Inc).

Results

A total of 13 892 patients newly diagnosed as having prostate cancer met the study inclusion criteria (**Figure**). The mean (SD) age at cohort entry was 72.1 (9.1) years, with a mean (SD) follow-up of 4.5 (3.1) years. The cohort was followed up for a total of 62 884 person-years, generating 2429 prostate cancer–specific deaths and 5001 deaths from any cause, with corresponding crude incidence rates of 3.86 (95% CI, 3.71-4.02) per 100 person-years and 7.95 (95% CI, 7.73-8.18) per 100 person-years, respectively.

There were a total of 574 patients (4.1%) who were prescribed 5-ARIs at least 12 months before their prostate cancer diagnosis, with 514 receiving finasteride and 60 receiving du-

tasteride. The median treatment duration before diagnosis was 12.8 months (range, 28 days to 12.6 years).

Table 1 presents the characteristics of the entire cohort and characteristics stratified by prediagnostic use and nonuse of 5-ARIs. Overall, users of 5-ARIs were older, more likely to have smoked, had higher BMIs, and were generally less healthy than nonusers. However, 5-ARI users were not more likely to have higher tumor grades (Gleason score, 8-10, 11.3% [user] vs 12.2% [nonuser]) or more likely to present with distant metastases at diagnosis compared with nonusers (Table 1).

Table 2 presents the results of the primary analysis. In the first model that adjusted for predefined covariates (conventional model), prediagnostic use of 5-ARIs was not associated with an increased risk of prostate cancer-specific mortality compared with nonuse (crude incidence rates, 3.76 [95% CI, 3.04-4.59] vs 3.87 [95% CI, 3.71-4.03] per 100 person-years, respectively; adjusted HR, 0.86; 95% CI, 0.69-1.06). Similar results were obtained in the HD-PS adjusted model (adjusted HR, 0.90; 95% CI, 0.73-1.13) (Table 2). Overall, there was no evidence that the use of 5-ARIs was associated with a higher cumulative incidence of prostate cancer-specific mortality, irrespective of tumor grade (eFigure in the Supplement).

The results for all-cause mortality are also presented in Table 2. In the conventional model, prediagnostic use of 5-ARIs was not associated with an increased risk of death from any cause compared with nonuse (crude incidence rates, 8.42 [95% CI, 7.32-9.64] vs 7.93 [95% CI, 7.71-8.16] per 100 person-years, respectively; adjusted HR, 0.87 [95% CI, 0.75-1.00]). A similar null effect was observed with the HD-PS adjusted model (adjusted HR, 0.92 [95% CI, 0.80-1.07]) (Table 2).

The association between 5-ARI cumulative duration of use and prostate cancer-specific and all-cause mortality is presented in **Table 3**. Overall, there was no duration-response relationship with either mortality outcome, with all the HRs of the tertile categories nonsignificant and around the null value (Table 3).

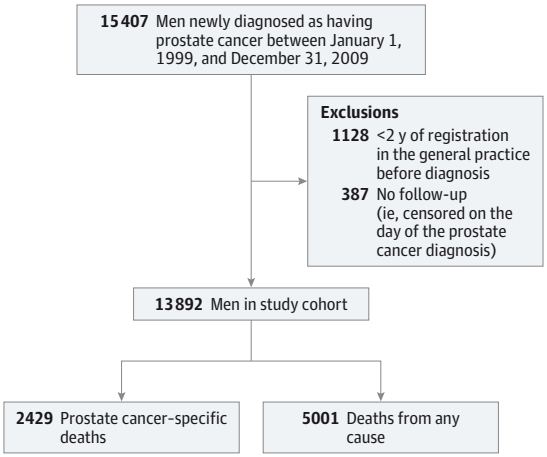
Sensitivity Analyses

Varying the length of the exposure lag window before cohort entry to 0, 6, and 24 months led to results consistent with those of the primary analysis (eTable 1 in the Supplement). A total of 9412 patients (67.8%) were initially registered with their general practice in or before 1992, the year the first 5-ARI was licensed in the UK. Restricting the analyses to this subcohort yielded similar results as those of the primary and secondary analyses (eTable 2 in the Supplement). Finally, the HR for prostate cancer-specific mortality did not materially change after accounting for competing risks due to deaths from other causes (adjusted subdistribution HR, 0.82 [95% CI, 0.65-1.04]).

Discussion

The results of this large population-based study indicate that prediagnostic use of 5-ARIs is not associated with an increased risk of prostate cancer-specific and all-cause mortality in men newly diagnosed as having prostate cancer. These

Figure. Flowchart of 13 892 Men With Newly Diagnosed Prostate Cancer Included in the Study Cohort



results remained consistent after performing several secondary and sensitivity analyses. Overall, these findings support the view that 5-ARIs do not increase the risk of high-grade tumors,[4-7,27,28] which would have translated into a higher prostate cancer-specific mortality risk.

It is important to note that our study addressed an important safety question related to the use of 5-ARIs, especially relevant for men with BPH. However, it was not designed to assess the effectiveness of 5-ARIs as chemopreventive agents. Such a study would have required determining whether the prostate cancer incidence risk reduction associated with these drugs also translates into a clinically meaningful reduction in prostate cancer-specific mortality. Thus, additional studies are needed to investigate this specific question, which is distinct from the one addressed in our study.

To our knowledge, only 3 observational studies have assessed the association between 5-ARIs and the risk of prostate cancer outcomes.[9-11] In one study of 1024 men who underwent radical prostatectomy, prediagnostic use of 5-ARIs was not found to be statistically associated with an increased risk of biochemical recurrence (HR, 1.03; 95% CI, 0.55-1.93).[10] That study was limited to only 50 patients previously exposed to 5-ARIs.[10] In another study of 1315 men who underwent radical prostatectomy, the use of 5-ARIs was not associated with an increased risk of biochemical recurrence (HR, 0.99; 95% CI, 0.70-1.40) or all-cause mortality (HR, 0.79; 95% CI, 0.37-1.65).[11] However, as with the previous study,[10] statistical power was limited, given the small size of the cohort and the few exposed cases (37 and 8 for biochemical recurrence and all-cause mortality, respectively). Finally, in 1 large study that included over 3 million men from Denmark, the use of ARIs was associated with an increased risk of prostate cancer-specific mortality (HR, 2.10; 95% CI, 1.97-2.30).[9] However, in a separate analysis, the authors reported that BPH and use of α-blockers were associated with similar increased risks,[9] suggesting that the observed association with 5-ARIs was potentially confounded by the indication. Finally, our results are in line with those of the recent post hoc analysis of the PCPT trial.[12] In that

Table 1. Baseline Characteristics of the Entire Cohort and Stratified According to Prediagnostic Use of 5-ARIs

Characteristic	Patients, No. (%)		
		Prediagnostic Use of 5-ARIs	
	Entire Cohort (N = 13 892)	Use (n = 574)	No Use (n = 13 318)
Age, mean (SD), y	72.1 (9.2)	76.2 (8.2)	71.9 (9.2)
Race/ethnicity			
White	11 607 (83.6)	511 (89.0)	11 096 (83.3)
Black	132 (1.0)	7 (1.2)	125 (0.9)
Other	151 (1.1)	7 (1.2)	144 (1.1)
Unknown	2002 (14.4)	49 (8.5)	1953 (14.7)
Excessive alcohol use	1053 (7.6)	49 (8.5)	1004 (7.5)
Smoking status			
Ever	7800 (56.2)	353 (61.5)	7447 (55.9)
Never	5406 (38.9)	209 (36.4)	5197 (39.0)
Unknown	686 (4.9)	12 (2.1)	674 (5.1)
BMI			
<18.5	116 (0.8)	4 (0.7)	112 (0.8)
18.5-25	3916 (28.2)	172 (30.0)	3744 (28.1)
25-30	5053 (36.4)	218 (38.0)	4835 (36.3)
≥30	1897 (13.6)	88 (15.3)	1809 (13.6)
Unknown	2910 (21.0)	92 (16.0)	2818 (21.2)
Charlson Comorbidity Index			
0	6492 (46.7)	213 (37.1)	6279 (47.2)
1-2	5448 (39.2)	235 (40.9)	5213 (39.1)
≥3	1952 (14.1)	126 (22.0)	1826 (13.7)
Ever-use of medication			
Aspirin	4559 (32.8)	258 (45.0)	4301 (32.3)
Other NSAIDs	8238 (59.3)	392 (68.3)	7846 (58.9)
Statins	3456 (24.9)	195 (34.0)	3261 (24.5)
α-Blockers	2489 (17.9)	350 (61.0)	2139 (16.1)
Prostate cancer–related variables			
PSA level at diagnosis, ng/mL			
<4	482 (3.5)	39 (6.8)	443 (3.3)
4-10	3147 (22.7)	120 (20.9)	3027 (22.7)
>10	6229 (44.8)	216 (37.6)	6013 (45.2)
Unknown	4034 (29.0)	199 (34.7)	3835 (28.8)
Gleason score			
2	42 (0.3)	2 (0.4)	40 (0.3)
3-6	2944 (21.2)	116 (20.2)	2828 (21.2)
7	2397 (17.3)	83 (14.5)	2314 (17.4)
8-10	1691 (12.2)	65 (11.3)	1626 (12.2)
Unknown	6818 (49.1)	308 (53.7)	6510 (48.9)
Distant metastases at diagnosis	1663 (12.0)	63 (11.0)	1600 (12.0)

Abbreviations: 5-ARIs, 5α-reductase inhibitors; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAIDs, nonsteroidal anti-inflammatory drugs; PSA, prostate-specific antigen.

SI conversion factor: To convert PSA to micrograms per liter, multiply by 1.

analysis, men initially randomized to finasteride were not more likely to die from any cause compared with placebo (adjusted HR, 1.03; 95% CI, 0.98-1.09).[12] Moreover, among the men diagnosed as having prostate cancer during the study period, those who received finasteride were not more likely to die from any cause (adjusted HR, 0.93; 95% CI, 0.78-1.12).[12] We note that the latter point estimate is remarkably similar to the one estimated in our HD-PS adjusted analysis for all-cause mortality (adjusted HR, 0.92; 95% CI, 0.80-1.07). Thus, while our study corroborates the results of PCPT post hoc analysis, it provides additional information with respect to prostate cancer-specific mortality, the clinical outcome of interest for men diagnosed as having prostate cancer.

This population-based study has a number of strengths. To our knowledge, this is one the largest observational studies to have investigated the association between the use of 5-ARIs and mortality outcomes in patients with prostate cancer in the natural setting of clinical practice. All cohort members were first identified in the NCDR, which likely maximized prostate cancer ascertainment.[29] Furthermore, with up to 14 years of follow-up, we were able to identify a considerable number of cases, and thus the study was well powered

Table 2. Crude and Adjusted HRs of Prostate Cancer–Specific and All-Cause Mortality Associated With the Use of 5-ARIs

Prediagnostic Use of 5-ARIs	No. Exposed	No. of Cases	Person-years	Incidence Rate (95% CI)[a]	Crude HR	Adjusted HR (95% CI)
Prostate Cancer–Specific Mortality						
Conventional model[b]						
No use	13 318	2338	60 461	3.87 (3.71-4.03)	1.00	1 [Reference]
Use	574	91	2423	3.76 (3.04-4.59)	0.96	0.86 (0.69-1.06)
HD-PS model[c,d]						
No use	12 848	2293	58 244	3.94 (3.02-4.61)	1.00	1 [Reference]
Use	574	91	2423	3.76 (3.04-4.59)	0.94	0.90 (0.73-1.13)
All-Cause Mortality						
Conventional model[b]						
No use	13 318	4797	60 461	7.93 (7.71-8.16)	1.00	1 [Reference]
Use	574	204	2423	8.42 (7.32-9.64)	1.05	0.87 (0.75-1.00)
HD-PS Model[c,d]						
No use	12 848	4732	58 244	8.12 (7.90-8.36)	1.00	1 [Reference]
Use	574	204	2423	8.42 (7.32-9.64)	1.03	0.92 (0.80-1.07)

Abbreviations: 5-ARIs, 5α-reductase inhibitors; HD-PS, high-dimensional propensity score; HR, hazard ratio.

[a] Per 100 person-years.

[b] The conventional model was adjusted for the following covariates: age, year of diagnosis, ethnicity, excessive alcohol use, smoking status, body mass index, Charlson Comorbidity Index, aspirin, other nonsteroidal anti-inflammatory drugs, statins, and α-blockers.

[c] A total of 470 men were trimmed from the unexposed group due to nonoverlap of the propensity score distributions.

[d] The HD-PS model was adjusted for age, year of diagnosis, and HD-PS deciles.

Table 3. Cumulative Duration of 5-ARI Use and the Risk of Prostate Cancer–Specific and All-Cause Mortality[a]

Prediagnostic Use of 5-ARIs	No. Exposed	No. of Cases	Person-years	Incidence Rate (95% CI)[b]	Crude HR	Adjusted HR (95% CI)[c]	*P* Value for Trend
Prostate Cancer–Specific Mortality							
No use	13 318	2338	60 461	3.87 (3.71-4.03)	1.00	1 [Reference]	.36
Use <210 d	188	23	903	2.55 (1.65-3.76)	0.68	0.68 (0.45-1.02)	
Use 210-879 d	253	44	1080	4.07 (3.00-5.42)	1.03	0.95 (0.70-1.29)	
Use >879 d	133	24	441	5.44 (3.57-7.97)	1.29	0.92 (0.62-1.39)	
All-Cause Mortality							
No use	13 318	4797	60 461	7.93 (7.71-8.16)	1.00	1 [Reference]	.26
Use <210 d	188	57	903	6.31 (4.83-8.12)	0.81	0.75 (0.58-0.98)	
Use 210-879 d	253	86	1080	7.96 (6.41-9.79)	1.00	0.84 (0.68-1.04)	
Use >879 d	133	61	441	13.83 (10.67-17.65)	1.66	1.07 (0.83-1.39)	

Abbreviations: 5-ARIs, 5α-reductase inhibitors; HD-PS, high-dimensional propensity score; HR, hazard ratio.

[a] The cumulative duration of use categories represent tertile categories.

[b] Per 100 person-years.

[c] Adjusted for age, year of diagnosis, ethnicity, excessive alcohol use, smoking status, body mass index, Charlson Comorbidity Index, aspirin, other nonsteroidal anti-inflammatory drugs, statins, and α-blockers.

to investigate the 2 outcomes of interest. This study also considered issues related to reverse causality and latency, thus avoiding minimizing bias. Finally, linking the NCDR, CRPD, HES, and ONS databases allowed us to collect and adjust for a number of potential important confounders, such as ethnicity, smoking, and BMI.

This study has some limitations. Prescriptions in the CPRD represent those issued by general practitioners; thus, misclassification of exposure is possible if patients did not comply with the treatment regimen or if they were treated by specialists. Misclassification with respect to prostate cancer–specific mortality is also possible. However, compared with other cancer types, prostate cancer–specific mortality has been shown to be generally well recorded in death certificates ($\kappa = 0.91$).[30] Furthermore, our prostate cancer–specific mortality rate of 3.86 per 100 person-years is concordant with rates previously reported in the UK.[31] Tumor stage information was missing for nearly 90% of patients, and there were missing data on Gleason scores and prostate-specific antigen levels. However, because these variables were thought to be causal intermediates (ie, the effect of 5-ARIs on prostate cancer–specific mortality is via tumor grade and stage), their inclusion in the models would have resulted in an overadjustment bias.[24] Finally, as with any observational study, residual confounding needs to be considered. Reassuringly, the results remained consistent in the HD-PS adjusted models, suggesting that residual confounding likely played a minor role in the null findings.

Conclusions

The results of this study indicate that the use of 5-ARIs before prostate cancer diagnosis is not associated with an increased risk of prostate cancer-specific and all-cause mortality. These findings should provide reassurance to patients with BPH who are treated with these drugs. Additional studies are warranted to assess the effectiveness of these drugs in preventing prostate cancer-specific mortality in men not previously diagnosed as having prostate cancer.

ARTICLE INFORMATION

Author Contributions: Dr Azoulay had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Azoulay, Benayoun.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Azoulay, Eberg, Pollak.
Critical revision of the manuscript for important intellectual content: Azoulay, Benayoun, Pollak.
Statistical analysis: Azoulay, Eberg.
Obtained funding: Azoulay.
Administrative, technical, or material support: Pollak.
Study supervision: Azoulay, Benayoun.

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