5-α REDUCTASE INHIBITORS in TREATMENT of BENIGN PROSTATIC HYPERPLASIA

5-α REDUCTASE INHIBITORS IN TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

By

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I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

Primary Mentor:

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Overview

Benign prostatic hyperplasia (BPH) is one of the most commonly diagnosed chronic diseases in older men associated with a gradual deterioration of lower urinary tract symptoms (LUTS). 5-α reductase inhibitors (5ARIs) are among the most commonly used pharmacological treatments for BPH(1, 2). They act by inhibiting the enzyme 5α-reductase, promoting prostatic apoptosis and prostate size reduction in order to improve urinary symptoms. Although multiple clinical trials showed 5ARIs could reduce the risk of AUR or need for surgery(3-7), In practice, poor adherence to 5ARIs treatment remains to be a problem, which could lead to a reduced efficacy. The relationship between levels of adherence and long-term clinical outcomes has not been determined.

Despite the fact that 5ARIs are widely used for benign prostatic hyperplasia, several preclinical studies have demonstrated that treatment with an anti-androgen such as 5ARIs could potentially decrease the incidence of bladder cancer(8, 9). Limited results from observational studies failed to reach a consensus on whether there was a difference in the incidence of bladder cancer between men who received 5ARIs and those who did not(10, 11).

In our study we utilized big data generated from medical claims by the Partners Center for Population Health Evaluation and Research Unit to investigate the effect of 5ARIs therapy on men diagnosed with BPH. In the first part of the study, we focused on evaluation of drug adherence and long-term clinical outcomes. In the second part, we investigated if 5ARIs therapy affect on bladder cancer incidence.

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Project 1: DRUG ADHERENCE AND CLINICAL OUTCOMES

Drug adherence and clinical outcomes in patients treated with 5-α reductase inhibitors treatment for benign prostatic hyperplasia

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Abstract

Purpose

Patients treated with 5-α reductase inhibitors (5ARIs) for benign prostatic hyperplasia (BPH) have poor adherence to medication. The aim of this study was to evaluate drug adherence and long-term clinical outcomes in patients treated with 5ARIs therapy for lower urinary tract symptoms related to benign prostatic hyperplasia.

Methods

We accessed longitudinal, pharmacy payment claim records from the Partners Healthcare System for the period from January 2009 to July 2018. We identified individuals with more than one dispensation of 5ARIs medicine for diagnosis of BPH and lower urinary tract symptoms. Adherence was calculated using proportion of days covered (PDC). We collected demographic and clinical variables during the first year since the initiation of 5ARIs. The outcome of the study was 5ARIs treatment failure defined by the occurrence of a BPH related surgery. A Cox proportional hazards model was used to estimate median time to 5ARIs treatment failure in high adherent and low adherent patients.

Results

Patients with low level of adherence to 5ARIs were more likely to need surgical intervention (95% CI: 1.02 to 1.59, p = 0.036) after adjusting for age, BPH stage, the presence of hematuria, bladder stone, and type of 5ARIs. The presence of bladder stone (HR = 1.70, 95% CI: 1.02 to 2.86, p = 0.043) is a significant risk factor for 5ARIs failure. As for types of 5ARIs, patients under dutasteride, compared to finasteride, are less likely to fail (HR = 1.42, 95% CI: 1.01 to 1.98, p = 0.044).

Conclusion

Low level of adherence to 5ARIs treatment in patients with BPH is associated with an increased risk of medication failure. Therefore, intervention strategies are needed to increase adherence to 5ARIs treatment after patients' diagnosis.

Introduction

Benign prostatic hyperplasia (BPH) is one of the most commonly diagnosed medical conditions in older men. U.S. population-based studies showed an age-related increase prevalence of BPH, which rises to nearly 50% in men by their eighth decade of life(1). BPH is a chronic disease associated with a gradual deterioration of lower urinary tract symptoms (LUTS). Pharmacological treatments such as alpha blockers and 5-α reductase inhibitors are commonly used to improve LUTS and to prevent serious outcomes such as acute urinary retention (AUR). Nevertheless when medical therapy fails, invasive interventions become necessary.

5-α reductase inhibitors (5ARIs) are among the most commonly used pharmacological treatments for BPH, particularly for patients with larger prostates(2, 3). They act by inhibiting the enzyme 5α-reductase, promoting prostatic apoptosis and prostate size reduction in order to improve urinary symptoms. In practice, poor adherence to 5ARIs treatment is a well-recognized problem. A study showed 1-yr adherence to 5ARIs treatment for BPH was only 29%, and patients on combined therapies had an even higher discontinuation rate(4). Although multiple clinical trials showed 5ARIs could reduce the risk of AUR or need for surgery(5-9), the efficacy might differ in a true community practice setting, since there will be less oversight and therefore worse adherence for patients who are treated with a study medication as compared to a clinical trial. The relationship between levels of adherence and long-term clinical outcomes has not been determined.

Claim data records medication dispenses, which can be a reliable source to evaluate medication adherence and indicate medication-refill behavior among patients with chronic diseases such as BPH(10-12). Besides, using direct claim data as a measure of medication adherence can eliminate potential recall bias. We conducted this study using population health management data, which included statistics on health status, health care utilization and costs for patients. The aim was to evaluate drug adherence and long-term clinical outcomes in patients administered 5ARIs therapy for LUTS related to benign prostatic hyperplasia.

Methods

Partners HealthCare in Boston, Massachusetts was founded by Brigham and Women's Hospital and Massachusetts General Hospital and has one of the biggest health care networks in North America including hospitals, community health centers, physician practices, and post-acute care facilities. The Partners Center for Population Health Evaluation and Research Unit is the source for data intended for research purposes, which includes complete administrative claims data (Medical and pharmacy) for approximately 1.2 Million Medicare Accountable Care Organization and Commercial risk contract patients. Comprehensive clinical information from each patient is generated during the course of patient care from multiple clinical and administrative computing systems. Information of BPH treatment such as pharmacy information, medical diagnoses, and initial visit information is captured. Computerized pharmacy records for 102,240 5ARIs prescriptions dispensed for 5,700 clinic patients were generated during the study period using the International Classification of Diseases (ICD) codes.

Twenty-three percent (n=5,700) of all patients who were diagnosed with BPH during the study period were prescribed with 5ARIs with claims that contain the following diagnosis codes: 600.0 to 600.3, and 600.9. Patients with more than one dispensation of 5ARIs medicine for a diagnosis of BPH (5ARIs medications included finasteride and dutasteride) commencing in the period January 2009 to December 2018 were enrolled in the study on the date their first prescription for 5ARIs was dispensed. Patients who received 5ARIs before July 2009 were excluded to ensure that all individuals had not been prescribed 5ARIs for at least six months before the initiation of 5ARIs treatment. Patients with a diagnosis of prostate cancer (185, 198.82, 233.4, 236.5, 239.5, V10.46) or bladder cancer (188, 198.1, 223.3, 233.7, 236.7, 239.4, V10.51) at any time during the follow up were also excluded from analysis.

Figure 1 demonstrates the study design scheme. We evaluated automated pharmacy records for the twelve months following the date 5ARIs was started. Adherence was calculated using Proportion of days covered (PDC) (13), which is supported by the International Society for Pharmaceutical Outcomes Research(14). PDC is defined as the ratio of days that a patient supplied with medication to the total number of days in a year (PDC1yr=[1-(days without medication)/365]). For example, PDC1yr =0.80 means that a patient had enough medication 80% of the time in the first year of 5ARIs treatment. High level of adherence to medication in chronic disease was defined as PDC $\geqslant$ 80% in many studies(15-17). Thus, we categorized adherence to

medication into binary outcomes, where patients with either high level of adherent (PDC ≥ 0.80) or low level of adherent (PDC < 0.80). We also conducted sensitivity analyses for adherence measured up to five years from the date 5ARIs was initiated.

Baseline information was collected on the date patients were dispensed with their first 5ARIs regimen including age, race, veteran status, marital status, education level, smoking status, and alcohol use. Pharmacy information was also collected including brand name, dosage, health provider information. Comorbidity within the first year of follow-up was evaluated based on the diagnosis data using ICD codes. Severity risk factors such as hematuria and bladder stones as well as hypertension, diabetes, erectile dysfunction, and mental disorder were included in the analysis. To measure BPH severity, BPH related complications were evaluated using the Thomson Medstat Disease Staging coding methods(18). This method is a coding criterion based on ICD diagnosis codes and supported by Healthcare Cost and Utilization Project as a classification system. Patients were categorized into non-complicated (stage 1) or complicated BPH (stage 2 or more) based on ICD codes during the first-year evaluation. Whether if presence with hematuria and/or bladder stones were also included to capture additional severity risks.

The outcome of the study was 5ARIs treatment failure defined by the occurrence of a BPH related surgery including surgical treatment and minimally invasive therapy using Current Procedural Terminology (CPT) codes (52601, 52612, 52614, 52620, 52640, 52647, 52648, 55801, 55821, 55831, 52850, 52852, and 52853). We evaluated the outcome starting one year after the initiation of 5ARIs. The time to 5ARIs treatment failure was defined as the time from the index date to the first BPH related surgery. All patients were followed until the 5ARIs failure, death, loss follow up, or reached the end of study (12/31/2018).

Distribution of categorical variable was examined by frequencies and percentages, and continuous variable was examined by means and standard deviation (SD). Univariate analysis comparing the two groups was performed using chi-square test for categorical variables and t-test for continuous variables. Cox proportional hazards regression analysis was performed to analyze the relative hazard ratio of 5ARIs treatment failure by the level of adherence to 5ARIs. First we computed univariate Cox analyses for all the baseline variables and 95% CIs and p value were calculated. Any variable had a significant univariate test based on the Wald test from

logistic regression and p-value cut-off point of 0.05 was selected for the multivariate analysis. Clinical relevant variables were also included in the model regardless of their significance in order to control for confounding. All analysis was done using STATA. We calculated two side p value and considered a value <0.05 as statistically significant.

Results

We identified 3,107 patients for study inclusion (Figure 2). The majority of the patients who initiated their first 5ARIs treatment during the study period were white males who were non-smoker and non-alcohol user with an average age of 77.5 (Table 1). 89.1% of the study cohort was treated with finasteride, and only 10.9% was treated with dutasteride. BPH stage, based on Thomson Medstat Disease Staging coding, was evaluated during the first year of the follow-up, 91.2% of patients were categorized as BPH stage 1 and 8.8% as stage 2 or more. 8% of the patients presented with hematuria and 3.3% with bladder stone. 23.5% of the study cohort was also diagnosed with hypertension, 9.1% with diabetes, 3.5% with mental disorder and 3.1% with erectile dysfunction. The mean follow-up time was 45.1 months, during which 373 (12.0%) received BPH related surgery (i.e., 5ARIs treatment failure).

As shown in the Kaplan-Meier curve in Figure 3, low level of adherence to 5ARIs was significantly associated with shorter time to 5ARIs failure (log-rank test p = 0.0372). The results of sensitivity analyses conducted using adherence measured up to five years were similar. When adjusted for age, BPH stage, presence of hematuria, bladder stone, and type of 5ARIs, Multivariate Cox proportional hazard regression analysis revealed the hazard ratio was 1.29 (95% CI: 1.04 to 1.62, p = 0.023) (Table 2). Moreover, we found that presence of bladder stone had (HR = 1.71, 95% CI: 1.02 to 2.87, p = 0.042) is a significant risk factor for 5ARIs treatment failure. As for types of 5ARIs, patients under finasteride, compared to dutasteride, are more likely to fail (HR = 1.42, 95% CI: 1.01 to 1.98, p = 0.044). Other factors including high BPH stage and presence of hematuria were related to poor outcome. However, they were not significant in the adjusted model.

Discussion

This study aimed to evaluate the impact of 5ARIs drug adherence on long-term clinical outcomes among a cohort of patients diagnosed with BPH. Among patients initiating their first 5ARIs regimen, we found that patients with low level of adherence is 29% more likely to need a BPH related surgery compared to those with high level of adherence.

5α-reductase is an enzyme that catalyzes the conversion of testosterone to 5α-dihydrotestosterone (DHT), which is involved in the pathogenesis of prostatic hyperplasia. 5ARIs including finasteride and dutasteride act as competitive and specific inhibitors of 5α-reductase to prevent conversion of testosterone to DHT, which ultimately reduces the prostate size(6, 19, 20) to relieve patients of bladder outlet obstruction. Multiple studies(21-23) suggested that prostate size was reduced to improve symptoms after 6 to 12 months. Clinical trials such as Proscar Long-Term Efficacy and Safety Study (PLESS) and The Medical Therapy of Prostatic Symptoms (MTOPS) Study have demonstrated that 5ARIs have the potential for long-term reduction in prostate volume and need for prostate surgery(4, 24). Nevertheless, other observational studies failed to show that 5ARIs therapy was effective in treating men with BPH(25, 26). One possible explanation is that findings from clinical trials cannot be generalized to men outside the study's entry criteria. Moreover, the ability of 5ARIs to prevent surgery require chronic treatment and in real-world setting patients under long-term treatment may exhibit worse adherence to the prescribed course of treatment compared to those under a clinical trial setting(27).

Our results are consistent with those of previous study from Cindolo et al(4). They reported that, among men aged 40 years old, one year adherence to 5ARIs treatment for BPH was 29% and discontinuation was an independent risk factor for hospitalization for BPH and BPH surgery (HR 1.65 and 2.80; $p < 0.0001$). The one year adherence to 5ARIs treatment in our study was 75%, which was much higher compared to those reported by Cindolo et al. Noted that in our study, the adherence level was measured by the proportion of days covered (PDC), which is supported by the International Society for Pharmaceutical Outcomes Research(14). In Cindolo's study it was measured as discontinuation. Nonetheless, adherence and discontinuation are different. Some patients who failed to show improvement early in the treatment and discontinued

may later restart the original treatment, and thus may have been inappropriately classified as non-adherent. Thus, discontinuation can only represent adherence when the level of adherence is very low(28).

We also found several factors that could influence the probability of 5ARIs treatment failure. These factors included higher BPH stage, the presence of bladder stone, and if the initiating treatment was finasteride. BPH stage defined by Thomson Medstat Disease Staging Criteria(18) was used to measure BPH severity. The majority of patients (91.2%) were characterized with stage 1 level of BPH severity (i.e., without bladder outlet obstruction, hydronephrosis, renal failure, sepsis, or shock). Patients categorized as stage 1 were less likely to fail compared to patients categorized as stage 2 or more. Whether if presence with hematuria and bladder stones were also included to capture additional severity risks(18). In our multivariable analysis, once the presence of hematuria and bladder stones was included, the information gained from the BPH stage was no longer statistically significant in predicting 5ARIs failure. Bladder stones are commonly associated with Bladder outlet obstruction (BOO), chronic urinary tract infection and neurogenic bladder(29). We showed the presence of bladder stones was a strong indicator for 5ARIs treatment failure.

We also found patients using dutasteride were 42% less likely to fail compared to finasteride. Dutasteride inhibits both type 1 and type 2 5α-reductase, while finasteride only inhibits type 2 isoenzyme. Study shows that dutasteride results in a significantly greater decrease in dihydrotestosterone compared to finasteride(30, 31). Nonetheless, meta-analysis showed that no statistically significant differences were detected in reducing the risk of AUR or need for surgery between two treatments(32). The inconsistent results could be contributed to longer to the imbalance between regimens: only 10.9% of the whole cohort was under dutasteride treatment.

We acknowledge that there are limitations to our analysis. Firstly, when we measured medication adherence with claim data, we assumed that patients consumed all medication as prescribed. Thus, we could overestimate the percentage of patients who are adherent to their medication. Secondly, there was selection bias since patients in our study were Medicare beneficiaries and they could not be selected unless they are eligible for Medicare (i.e.: ≥ 65 years). The results could be different among younger patients. Thirdly, although we adjusted our results using BPH

stage generated by diagnosis information, diagnostic test, and biochemical results were missing. Variations in BPH severity between different adherent groups are likely. Drug adherence could be influenced by the indicators of BPH severity, such as prostate size and PSA level. Although it is uncertain that patient with the more severe condition tends to cautiously adhere to the drug or tends to discontinue after failing to show improvement, it would be useful to link actual prostate size or PSA level to each. A recent study suggested one-third of men were resistant to 5ARI therapies(33), who might show certain genetic traits. Additional biochemical information would also be helpful to shed light on the profile of those who fail 5ARIs therapy. Factors associated with increased levels of inflammatory mediators such as obesity and age could indicate a group of patients that may not be responsive to 5ARIs(34). Finally, although we adjusted our results for common risk factors of BPH surgery such as age, BPH severity, and comorbidity, we could not adjust for all potential risk factors of BPH surgery such as socioeconomic factors, which can affect population's overall health outcomes.

Conclusion

In conclusion, low level of adherence to 5ARIs treatment in patients with BPH is associated with an increased risk of medication failure. Therefore, intervention strategies are needed to increase adherence to 5ARIs treatment after patients are diagnosed.

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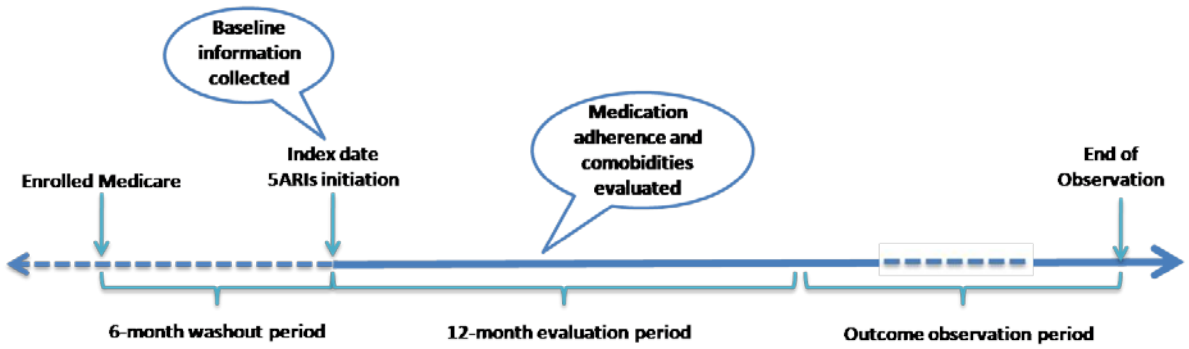

Figure 1. Study Design Scheme

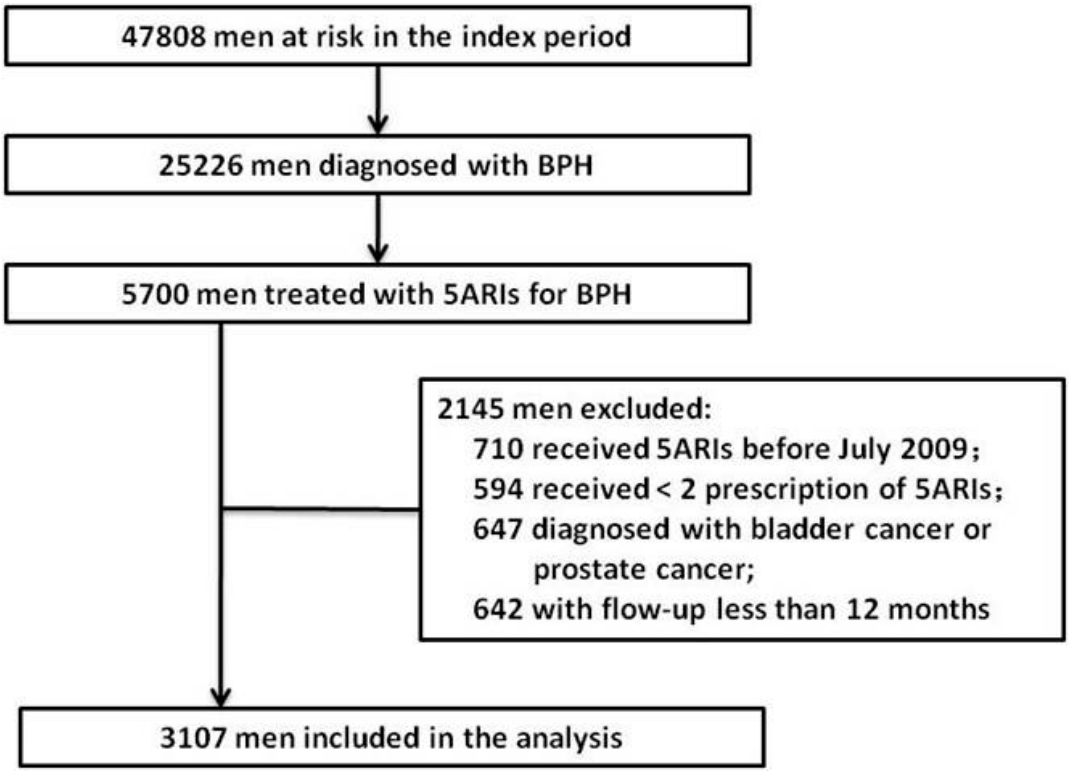

Figure 2. Sample selection flowchart

Table 1. Patient demographics and clinical characteristics

Characteristics	Values	(%)
No. patients	3107	
Medication adherence (first year)		
High (PDC≥0.8)	2327	74.9
Low (PDC<0.8)	780	25.1
Age (year)		
<70	554	17.8
70-79	1516	48.8
≥80	1037	33.4
Race		
White	2587	83.3
Others	225	7.2
Unknown	295	9.5
Veteran Status		
Yes	1023	32.9
No	1412	45.4
Unknown	672	21.6
Marital Status		
Single	758	24.4
Married	2008	64.6
Unknown	341	11.0
Education Level		
High school or below	951	30.6
College or above	1140	36.7
Unknown	1016	32.7
Alcohol use		
No	1051	33.8
Yes	785	25.3
Unknown	1271	40.9
Tobacco use		

Never	980	31.5
Quit	1547	49.8
Yes	168	5.4
Unknown	412	13.3
BPH stage		
Stage 1	2834	91.2
Stage 2 or more	273	8.8
Presence of hematuria		
No	2859	92.0
Yes	248	8.0
Presence of bladder stone		
No	3004	96.7
Yes	103	3.3
Type of 5ARIs		
Dutasteride	339	10.9
Finasteride	2768	89.1
Combined therapy		
No	2855	91.9
Yes	252	8.1
Comorbidity		
Diabetes	283	9.1
Hypertension	729	23.5
Mental Disorder	110	3.5
Erectile dysfunction	96	3.1

PDC = Proportion of days covered

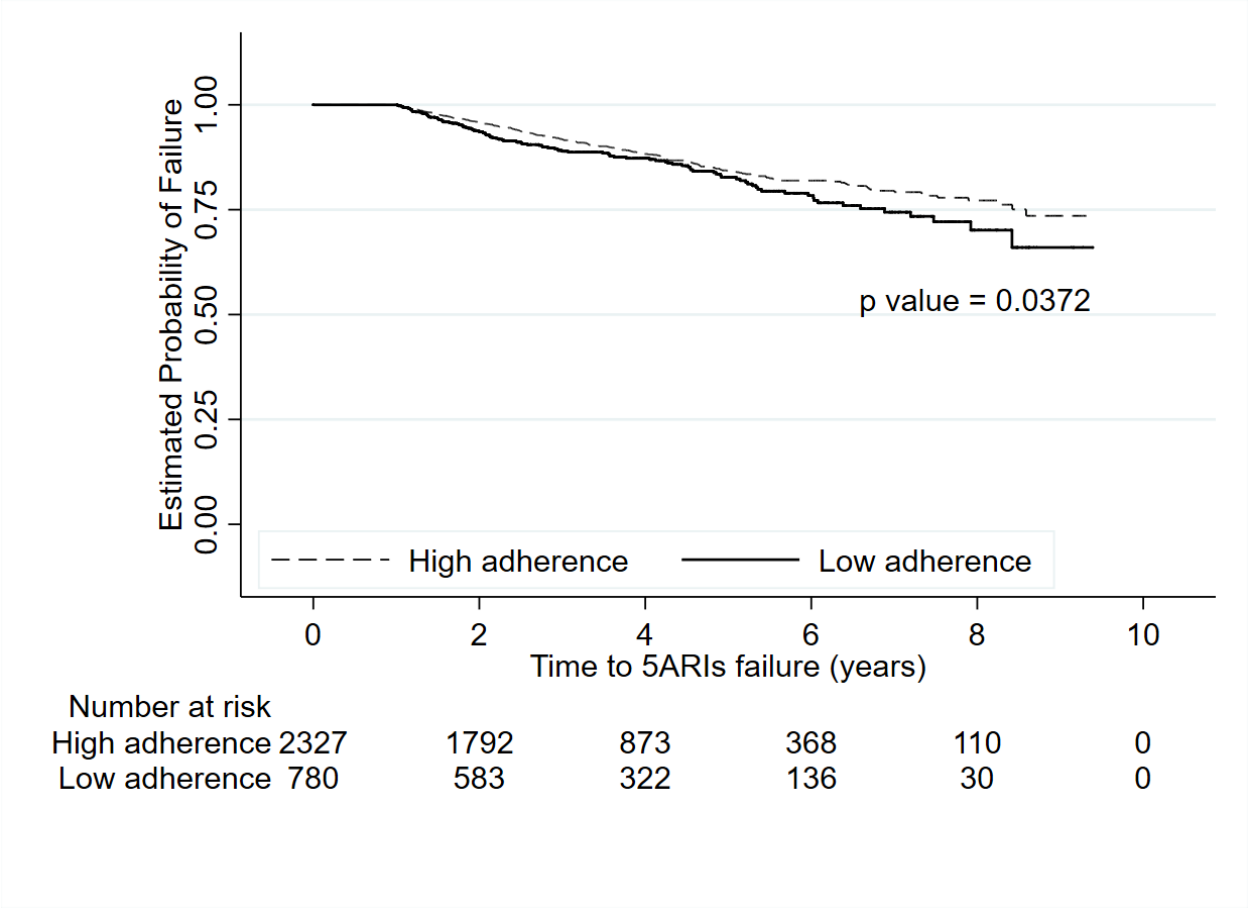

Figure 3. Time to 5ARIs failure by level of medication adherence. Log-rank test, p value = 0.0372. 5ARIs = 5-α reductase inhibitors.

Table 2. Cox model measured hazard ratio and 95% confidence intervals of BPH related surgery

Characteristics	Crude				Adjusted			
	HR	CI		p value	HR	CI		p value
Medication adherence (first year)								
High (PDC>=0.8)	1			Ref	1			Ref
Low (PDC<0.8)	1.26	1.01	1.58	0.038	1.29	1.04	1.62	0.023
Age								
<70	1			Ref	1			Ref
70-79	1.01	0.77	1.34	0.925	0.97	0.73	1.29	0.851
≥80	1.17	0.87	1.58	0.290	1.14	0.85	1.54	0.390
Race								
White	1			Ref				
Others	0.91	0.61	1.36	0.640				
Marital Status								
Single	1			Ref				
Married	0.97	0.76	1.23	0.810				
Education Level								
High school or below	1			Ref				
College or above	0.82	0.64	1.05	0.117				
Tobacco use								
Never	1			Ref				
Quit	0.94	0.75	1.18	0.600				
Yes	0.93	0.59	1.48	0.770				
Alcohol use								
No	1			Ref				
Yes	0.89	0.68	1.17	0.406				
Veteran Status								
No	1			Ref				
Yes	0.89	0.70	1.13	0.333				
BPH stage								

Stage 1	1			Ref	1			Ref
Stage 2 or more	1.57	1.10	2.25	0.012	1.38	0.95	1.98	0.090
Diabetes								
No	1			Ref				
Yes	1.03	0.70	1.54	0.849				
Hypertension								
No	1			Ref				
Yes	0.88	0.68	1.14	0.334				
Mental Disorder								
No	1			Ref				
Yes	1.33	0.75	2.36	0.960				
Erectile dysfunction								
No	1			Ref				
Yes	1.13	0.64	2.02	0.669				
Presence of hematuria								
No	1			Ref	1			Ref
Yes	1.42	0.98	2.05	0.065	1.24	0.85	1.83	0.264
Presence of bladder stone								
No	1			Ref	1			Ref
Yes	1.86	1.12	3.07	0.015	1.71	1.02	2.87	0.042
Type of 5ARIs								
Dutasteride	1			Ref	1			Ref
Finasteride	1.41	1.01	1.97	0.045	1.42	1.01	1.98	0.044
Combined Therapy								
No	1			Ref				
Yes	1.08	0.78	1.49	0.635				

PDC = Proportion of days covered

Project 2: 5-α REDUCTASE INHIBITORS & BLADDER CANCER

5-α reductase inhibitors do not suppress the risk of bladder cancer in men with benign prostatic hyperplasia

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Abstract

Purpose

It has been hypothesized that 5-α reductase inhibitors (5ARIs), finasteride and dutasteride prevent the development of bladder cancer. However, a few of observational studies had inconsistent results,, which might be attributable to bias. The aim of this study was to investigate if 5ARIs therapy affect on bladder cancer based on database of claim data.

Methods

We accessed longitudinal, pharmacy payment claim records from the Partners center for the period from January 2012 to December 2018. We identified men aged 65 and above who had claims data that contained diagnosis of BPH. The intervention of interest was being prescribed 5ARIs medication finasteride and dutasteride and the outcome of interest was incident of bladder cancer. Potential confounders included age, smoking status (never, former, or current) and concurrent chronic diseases. A set of emulated trials were generated and eligibility criteria were applied. We pooled all trials data and performed a Cox proportional hazards regression analysis to estimate the emulated intention-to-treat hazard ratio (HR) of bladder cancer for 5ARIs initiators versus 5ARIs non-initiators controlling for baseline confounders.

Results

We identified 51,043 eligible person-trials from 18,369 unique individuals for study inclusion. During 155,191 person-years of follow-up, there were 1,114 new cases of bladder cancer and 6,256 deaths. The HR (95% CI, p) for the intention-to-treat effect of 5ARIs on bladder cancer was 1.00 (0.76-1.31, 0.982) after adjusted for baseline covariates. The HR (95% CI, p) was 1.01 (0.77-1.34, 0.893) for finasteride initiators compared with finasteride non-initiators, and 0.87 (0.40-1.89, 0.728) for dutasteride initiators when compared with dutasteride non-initiators.

Conclusion

Analysis of our claim data does not support the hypothesis that 5ARIs suppress the risk of bladder cancer.

Introduction

Several preclinical studies have demonstrated that the androgen receptor (AR) plays a potential role in modulating the development and progression of bladder cancer(1-5). Treatment with an anti-androgen has been suggested to decrease the incidence of bladder cancer in animal models(3, 6). 5-α reductase inhibitors (5ARIs) including finasteride and dutasteride are widely used for treating benign prostatic hyperplasia by competitively inhibits the conversion of testosterone to dihydrotestosterone(7). Because of its pharmacological mechanism, it was hypothesized that 5ARIs could prevent the development of bladder cancer. A secondary analysis of Prostate, Lung, Colorectal, and Ovarian (PLCO) trial(8, 9) showed less bladder cancer was diagnosed among those who reported finasteride compared to no use during the trial (hazard ratio: 0.634; 95% confidence interval, 0.493–0.816; p = 0.0004) (10). However, a more recent study found no difference in the incidence of bladder cancer between men who received finasteride and those who did not(11).

Part of the inconsistent results from previous studies(10, 11) might be attributable to bias from the nature of the secondary analysis because the existing data from the original randomized trials were not collected to address the particular research question or to test the particular hypothesis. But given the fact that bladder cancer diagnosis is rare, it may not be feasible, ethical, or timely to design a randomized trial. In cases like this, we can utilize real-world evidence to emulate the target trial of interest(12).

The primary aim of this study is to investigate the effect of 5ARIs therapy on bladder cancer from a database of claim data generated by the Partners Center for Population Health Evaluation and Research Unit.

Methods

Partners HealthCare in Boston, Massachusetts was founded by Brigham and Women's Hospital and Massachusetts General Hospital and has one of the biggest health care networks in North America including hospitals, community health centers, physician practices, and post-acute care

facilities. The Partners Center for Population Health Evaluation and Research Unit is the source for data intended for research purposes, which includes complete administrative claims data (Medical and pharmacy) for approximately 1.2 Million Medicare ACO and Commercial risk contract patients. Comprehensive clinical information from each patient is generated during the course of patient care from multiple clinical and administrative computing systems. Information on BPH treatment such as pharmacy information, medical diagnoses, and initial visit information is captured. Computerized records for 25,226 clinic patients were generated during the study period using the International Classification of Diseases (ICD) codes.

We started the follow-up on 1 January 2012 and followed patients through 31 December 2018. We included men aged 65 and above who had claims that contained the diagnosis codes of BPH (with ICD codes: 600.0 to 600.3, and 600.9) during the study period. Patients who had been diagnosed with bladder cancer (with ICD codes: 188, 198.1, 223.3, 233.7, 236.7, 239.4, V10.51), had been prescribed any 5ARIs in the past one year or had less than one year of continuous recording in the database were excluded.

The intervention of interest was being prescribed 5ARIs medication including finasteride and dutasteride and the outcome of interest was incident bladder cancer. Potential confounders included age, smoking status (never, former, or current) and concurrent chronic diseases.

In order to conduct a causal analysis of observational data, we generated a set of emulated trials(12). For the duration of the first year of the study (January 2012 to December 2012), eligibility criteria were applied. Patients started using 5ARIs during the year were categorized as initiators and followed from the date their first prescription for 5ARIs was dispensed. Those who did not start 5ARIs therapy were considered non-initiators and followed from the date they were diagnosed with BPH. Non-initiators, as well as initiators who discontinued 5ARIs therapy for at least one year, were eligible for the second emulated trial in 2013 (January 2013 to December 2013). In total, we generated six emulated trials (from 2012 to 2017) and followed patients until the occurrence of bladder cancer, death, loss follow up, or reached the end of study (2018/12/31).

We pooled the data from all trials. Distribution of categorical variable was examined by frequencies and percentages, and continuous variable was examined by means and standard

deviation (SD). Univariate analysis comparing the two groups was performed using chi-square test for categorical variables and t-test for continuous variables. Cox proportional hazards regression analysis was performed to estimate the emulated intention-to-treat hazard ratio (HR) of bladder cancer for 5ARIs initiators versus non-initiators controlling for baseline confounders. We used a robust variance estimator because the same patient could potentially participate in multiple trials. All analysis was done using STATA.

Results

We identified 51,043 eligible person-trials from 18,369 unique individuals for study inclusion, and Figure 4 presents a flow chart of the selection process. Table 3 shows their characteristics by 5ARIs initiation status. On average, the 5ARIs initiators were 1.0 years older than the non-initiators. A larger proportion of 5ARIs initiators had a past medical history of diseases such as diabetes, hypertension, mental disorder, and erectile dysfunction compared with non-initiators.

During 155,191 person-years of follow-up, there were 1,114 new cases of bladder cancer and 6,256 deaths. The median time of follow-up was 35.5 months among 5ARIs initiators and 36.6 months among non-initiators. The crude incidence rate of bladder cancer was 8.65 per thousand person-years among initiators and 7.07 among non-initiators. Table 4 shows the results of the intention-to-treat analysis. The HR (95% CI, p) for the effect of 5ARIs on bladder cancer was 1.14 (0.80-1.56, 0.306) before adjustment and 1.00 (0.76-1.31, 0.982) after adjusted for baseline covariates in Table 3. During the follow-up, 397 unique patients among 5ARIs initiators and 2.360 among non-initiators died. There was no significant difference in mortality between the two groups. HR (95% CI, p) was 0.95 (0.86-1.05, 0.279). Of all 5ARIs initiators, 84.0% used finasteride and 16.0% dutasteride. Table 5 showed the adjusted HR of bladder cancer for initiation of each 5ARIs. The HR was 1.01 (0.77-1.34, 0.893) for finasteride and 0.87 (0.40-1.89, 0.728) for dutasteride.

Discussion

The results of our study showed there was no difference in the risk of bladder cancer between 5ARIs initiators and non-initiators among men over 65 years old with BPH. No significant differences were observed with finasteride and dutasteride, the most commonly used 5ARIs in this population. We found the motility between 5ARIs initiators and non-initiators was similar. There was no evidence that death as a competing risk would have changed the results.

The incidence rate of bladder cancer in our study was significantly higher compared to those reported among general population(13) and similar compared to those reported by Sathianathen, et al(11). Patients in both our study and Sathianathen's were elderly male, which contributed to the high incidence as bladder cancer is age related and occurs more often in men than in women(13). Our results are consistent with those of the previous study from Sathianathen, et al(11), a secondary analysis on Medical Therapy for Prostatic Symptoms (MTOPS) Study(14). They categorized all patients enrolled in the MTOPS study into groups based on receiving finasteride or not and found there was no difference between groups in the risk of bladder cancer. As acknowledged by the authors, the results could be biased due to the small number of bladder cancer diagnoses (n = 18) during the limited follow-up. In our emulated trials, we were able to utilize big data to identify 476 unique cases of bladder cancer among 18,369 individuals with BPH with a median follow up time of 3.98 years. To further increase the efficiency of our estimate, we conceptualized our study as a sequence of "trials" starting at each subsequent year (2012, 2013, …, 2017) and then pooled data into a single analysis as described by Hernán, et al(12). Hence, we were able to show the effect of longer-term finasteride administration and greater statistical power. Moreover, the previous studies(11) did not include patients treated with Dutasteride, which is a dual 5α-reductase inhibitor resulting in a significantly greater decrease in dihydrotestosterone compared to finasteride(15, 16). Therefore, those findings of finasteride may not be generalized to dutasteride. Our analysis, to our knowledge, was the first study to include both finasteride and dutasteride. We also adjusted our analysis based on patients' demographic characteristics including smoking status, which is a crucial risk factor for bladder cancer(17).

Several animal models proposed biological mechanisms for the protective effects of the androgen receptor modulation, including androgen deprivation therapy (ADT) on bladder cancer(3, 6, 18, 19). Also, androgen receptor expression was found to be inversely correlated to

bladder cancer grade and stage(20, 21). In our study, there was not enough evidence to support those hypotheses. One possible explanation is that 5ARIs have different pharmacological effects compared to other androgen receptor modulators(22) and the bladder carcinogenesis may not be mediated by the conversion of testosterone to dihydrotestosterone.

We acknowledged that there were limitations to our analysis. First, our study is an observational study based on claims data, and thus, unmeasured confounding might affect results. Nonetheless, we conceptualized the observational database as if it were a sequence of nonrandomized "trials" by mimicking the design of the randomized trial as closely as possible. Secondly, since patients in our study were Medicare beneficiaries diagnosed with BPH, and they could not be selected unless they are eligible for Medicare (mainly ≥ 65 years), the finds might not be generalizable to other population. However, older man represents a population which is highly susceptible to bladder cancer(23, 24). Finally, although we were able to adjust for some common risk factors of bladder cancer such as age and tobacco use, we did not have data of all risk factors of bladder cancer such as certain chemicals exposure. The database did not include any information on tumor characteristics either, which made it impossible to further examine 5ARIs and bladder cancer progression. Even with its limitations, this is one of the few providing insights into 5ARIs and the risk of bladder cancer.

Conclusion

In summary, our results demonstrated that 5ARIs including finasteride and dutasteride does not prevent bladder cancer.

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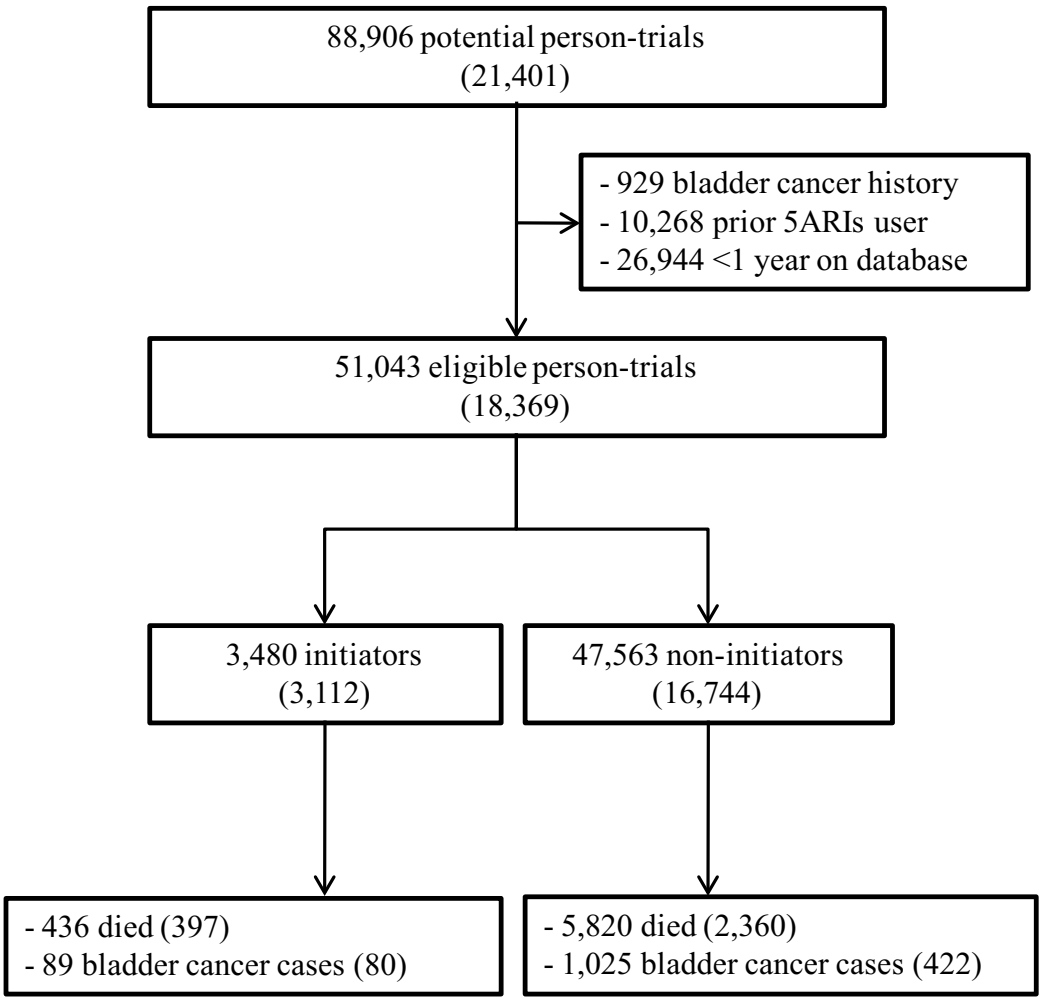

Figure 4- *Sample selection flowchart: PHM database 2012–2018. Numbers in parentheses indicate unique individuals.*

Table 3-*Characteristics of initiators and non-initiators of 5ARIs therapy at the start of the trial's follow-up: PMH database 2012–2018*

Characteristic	Non-initiators (47,563 person-trials)	Initiators (3,480 person-trials)	p
Age (yrs), mean (SD)	77.2(6.7)	78.2(6.9)	<0.01
Smoking status, n (%)			0.32
Never smoker	21561(45.3)	1593(45.8)	
Former smoker	18735(39.4)	1310(37.6)	
Current smoker	2608(5.5)	181(5.2)	
NA	4659(9.8)	396(11.4)	
Race, n (%)			0.02
White	41613(87.5)	2965(85.2)	
Others	2545(5.4)	227(6.5)	
NA	3405(7.2)	288(8.3)	
College or higher education n (%)			0.73
No	14292(30)	1056(30.3)	
Yes	19769(41.6)	1436(41.3)	
NA	13502(28.4)	988(28.4)	
Past medical history, n (%)			
Diabetes	5480(11.5)	415(11.9)	0.47
Hypertension	18307(38.5)	1311(37.7)	0.34
Mental Disorder	1793(3.8)	200(5.7)	<0.01
Erectile dysfunction	3171(6.7)	228(6.6)	0.80
Hematuria	3411(7.2)	435(12.5)	<0.01
Bladder stone	1791(3.8)	162(4.7)	<0.01
Prostatitis	862(1.8)	88(2.5)	0.03
Renal failure	979(2.1)	130(3.7)	<0.01
Urinary tract infection	2441(5.1)	296(8.5)	<0.01

5ARIs = 5-α reductase inhibitors; NA = not applicable.

Table 4-*HR (95% CI, p) for the analog of the intention-to-treat effect of 5ARIs on bladder cancer: PMH database 2012–2018*

Analysis	ITT, HR (95% CI, p)
Non-initiators	Reference
5ARIs initiators	
Unadjusted	1.14 (0.80-1.56, 0.306)
Adjusted for baseline variables[a]	1.00 (0.76-1.31, 0.982)

5ARIs = 5-α reductase inhibitors; ITT = intention-to-treat.

[a] Adjusted for baseline covariates in Table 3.

Table 5-*Type of 5ARIs and adjusted intention-to-treat HR (95% CI) for bladder cancer: PMH database 2012–2018*

Types of 5ARIs	Initiators (%)	Cases among initiators	ITT, HR (95% CI, p)
Finasteride	2922 (84.0)	73	1.01 (0.77-1.34, 0.893)
Dutasteride	558 (16.0)	16	0.87 (0.40-1.89, 0.728)

5ARIs = 5-α reductase inhibitors; ITT = intention-to-treat.

Summary

In the first project, we first identified 3107 individuals treated with 5ARIs medicine for diagnosis of BPH between 2009 and 2018. We measured adherence using proportion of days covered (PDC). We collected demographic and clinical variables during the first year since the initiation of 5ARIs. The outcome of the study was 5ARIs treatment failure defined by the occurrence of a BPH related surgery. A Cox proportional hazards model showed patients with low level of adherence to 5ARIs were more likely to need surgical intervention (95% CI: 1.02 to 1.59, p = 0.036) after adjusting for age, BPH stage, the presence of hematuria, bladder stone, and type of 5ARIs. Therefore, intervention strategies are needed to increase adherence to 5ARIs treatment after patients' diagnosis.

In the second project, we compared those individuals initiated 5ARIs treatment for BPH, who had not been diagnosed with bladder cancer to those who diagnosed with BPH during the same study period without any prescription of 5ARIs. After adjusted by potential confounders including age, smoking status, and concurrent chronic diseases, we found there was no difference in the risk of bladder cancer between 5ARIs initiators and non-initiators among men over 65 years old with BPH.

Discussion and perspectives

Our study found that patients with low level of adherence are 27% more likely to need a BPH related surgery compared to those with high level of adherence. This is one of the few studies providing insight into drug adherence and the impact on clinical outcome for 5ARIs treatment for BPH. Our results are consistent with those of previous study from Cindolo et al(1). Nonetheless, they measured adherence level using discontinuation, while we used the proportion of days covered (PDC). Adherence and discontinuation are different(2), as some patients who failed to show improvement early in the treatment and discontinued may later restart the original treatment, and thus may have been inappropriately classified as non-adherent.

We further investigated whether 5ARIS affect bladder cancer. The results of our study showed there was no difference in the risk of bladder cancer between 5ARIs initiators and non-initiators among men over 65 years old with BPH. Our finds suggest that bladder carcinogenesis may not be mediated by the conversion of testosterone to dihydrotestosterone. Compared to previous studies(3, 4), we were able to utilize big data to show the effect of longer-term finasteride administration and greater statistical power. Moreover, to our knowledge, our study was the first study to include both finasteride and dutasteride. We also adjusted our analysis based on patients' demographic characteristics including smoking status, which is a crucial risk factor for bladder cancer(5).

There are limitations as our study is an observational study based on claims data, including selection bias, unmeasured confounding and missing information on common risk factors that could affect the outcomes. However, we believe, even with its limitations, this study is one of the few providing insights into 5ARIs therapy and clinical outcomes.

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