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Risk of Type 2 Diabetes Mellitus in New Users of 5-Alpha Reductase Inhibitors: A Nationwide Historical Cohort Study

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Purpose: Recent large-scale studies have investigated the risk of type 2 diabetes mellitus (T2DM) associated with the use of 5-alpha reductase inhibitors (5-ARIs) in benign prostatic hyperplasia (BPH) patients, but heterogeneous findings have been reported. This study aimed to examine the risk of T2DM associated with 5-ARIs (finasteride and dutasteride) compared to tamsulosin.
Materials and Methods: We identified nationwide cohorts of new users of finasteride, dutasteride, and tamsulosin without a history of prescriptions for 5-ARIs or tamsulosin within the previous 3 years among patients covered by national health insurance between 2010 to 2020 in South Korea. Patients were free of T2DM and had received at least 90 days of dispensation of the medications. We balanced cohorts on risk factors for T2DM based on age, health insurance status, index year, comorbidities, and co-medications using stabilized inverse probability of treatment weighting. Adjusted hazard ratios (HRs) were estimated using Cox proportional hazards models, with censoring for treatment discontinuation, switching, or augmentation, end of enrollment, and death.
Results: A total of 34874 tamsulosin users, 16953 finasteride users, and 19480 dutasteride users were included. The adjusted HR for finasteride was 1.06 [95% confidence interval (CI), 1.01–1.11] and that for dutasteride was 0.97 (95% CI, 0.92–1.02), when compared with tamsulosin users. These estimates were consistent in lag time analyses and attenuated among patients with good compliance.
Conclusion: This study suggests minimal effects of finasteride and dutasteride on the risk of T2DM when compared with tamsulosin among patients with BPH.

Key Words: Finasteride, dutasteride, tamsulosin, pharmacoepidemiology

INTRODUCTION

Finasteride and dutasteride, both 5-alpha reductase inhibitors (5-ARIs), are widely used medications for the treatment of benign prostatic hyperplasia (BPH). In the UK alone, it is estimated that there are 3600000 prescriptions for finasteride annually.[1] Although initially demonstrated to be safe and efficacious through clinical trials,[2-4] post-marketing authorization studies have recently emerged highlighting a wide range of side effects associated with 5-ARIs. These side effects range from well-recognized problems such as sexual dysfunction[5,6] to more recently recognized neuropsychiatric symptoms[7] and metabolic disturbances[8] associated with long-term use of finasteride. Given the widespread use of these medications, these novel side effects need to be thoroughly investigated to avoid a potential public health hazard.

Multiple epidemiological studies have examined the risk of type 2 diabetes mellitus (T2DM) in patients taking 5-ARIs,[8-10] particularly finasteride and dutasteride. This relation was examined because accumulated in vitro observations and small clinical trials have suggested that inhibition of 5-alpha reduc-

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tase enzymes in men may increase the risk of T2DM by promoting body fat accumulation, reducing insulin sensitivity in adipose tissue via suppression of non-esterified fatty acids, and contributing to liver steatosis.[11] Nevertheless, the results of epidemiological studies have been heterogeneous, possibly due to methodological differences.[8-10] For example, a report by Lee, et al.[9] estimated the risk of new-onset T2DM at approximately 0.72 when comparing 5-ARIs users and non-users in the Taiwanese data. Using the same database, Wei, et al.[8] reported a 49% higher risk of new-onset T2DM in 5-ARIs users compared with tamsulosin users. Methodologically, the earlier study used a non-active comparator, which is susceptible to confounding by indication and healthy user bias. Although the later study used an active comparator (i.e., tamsulosin users), the authors did not mention a specific washout period, which might have introduced prevalent users into the new-user groups. If the effects of 5-ARIs were dose-dependent, including prevalent users could inflate the risk of developing T2DM. Given the popularity and long-term use of 5-ARIs to manage these conditions, their safety is an issue of great interest for both clinical practice and public health.

Therefore, there remains a need for large pharmacoepidemiologic studies with robust methods to replicate previous findings. We aimed to examine the risk of developing T2DM in BPH patients who initiated finasteride/dutasteride monotherapy in comparison to tamsulosin monotherapy based on a large-scale historical cohort of 5-ARIs new users in South Korea.

MATERIALS AND METHODS

Data source

For the purpose of this study, the Health Insurance Review and Assessment Service (HIRA) provided healthcare utilization data for all patients with at least one diagnostic code for BPH [International Classification of Diseases, 10th Revision (ICD-10) code N40] in primary and/or secondary positions between January 1, 2010, and December 31, 2020, in South Korea. The data include demographics (age and sex), all inpatient and outpatient claims for healthcare utilization and medications, insurance status (healthcare insurance or medical aid beneficiaries), and mortality data based on treatment results.[12] Data linkage was performed using de-identified unique identifiers. As such, the Institutional Review Board of Yonsei University Health System approved the waiver of informed consent (No. 4-2022-1549).

Study cohorts

We established a historical cohort of new users of finasteride, dutasteride, or tamsulosin for BPH in several steps (Supplementary Fig. 1, only online). First, after applying the 3-year washout period (from January 2010 to December 2012), we identified the first dispensed prescription for finasteride or dutasteride (hereafter collectively referred to as 5-ARIs) or tamsulosin from January 2013 for each patient. The date of the first prescription was set as the index prescription date (follow-up start date). From this cohort, we selected patients with at least one diagnosis code for BPH during the 3-year period prior to the index date. We then excluded patients with a diagnosis code for T2DM (ICD-10, E11) and/or a record of oral antidiabetic medication use during the 3-year period prior to the index date, patients treated with any 5-ARIs or tamsulosin within 3 years before the index date, patients with diagnosis codes for cancer (except for skin cancer; ICD-10, C43, and C44), and patients with diabetes mellitus other than T2DM (ICD-10 codes E10, E12, E13, and E14) during the entire study period. Tamsulosin users were selected as the control group to mitigate potential confounding by indication, as the 5-ARIs and tamsulosin are pharmacological treatments for BPH. This approach ensured that both groups consisted of individuals with a comparable underlying indication for treatment. Furthermore, prior research has shown that tamsulosin users did not have an increased risk of T2DM compared to BPH patients receiving surgical treatment.[8]

To ensure that we included patients who adhered to prescriptions and continuously used the drugs of interest, we selected patients with at least 90 dispensed days of one of the study drugs within 180 days from the index prescription. The 90-dispensed-day period was a grace period accounting for pill-cutting, forgetting to fill medications, or late prescriptions. In addition, based on the pharmacokinetics of finasteride and dutasteride, a 6-month period (180 days) should be a sufficient time for 99% of the drugs (5 half-lives) to be excreted from the circulation.[12,13] Finally, we excluded patients who had a diagnosis of T2DM and/or were using oral diabetic medication within 1 month after the index date. This 1-month period was used as a minimum induction period based on a prior study reporting increased hepatic insulin resistance in men after 3 weeks of treatment with dutasteride.[14] This is not to be confused with immortal time bias, which could arise from differences in baseline risk due to "selective timeline" induction. We believe that including this minimum induction time would guard our results against long-latent T2DM. Given that finasteride is a selective inhibitor reducing dihydrotestosterone concentrations primarily in the prostate, and dutasteride is a more potent dual inhibitor with systemic effects,[15] we performed separate analyses for finasteride and dutasteride. Two separate study cohorts, tamsulosin—finasteride and tamsulosin—dutasteride, were created for head-to-head comparisons of monotherapy effects. If a patient had records for both drugs (tamsulosin–finasteride/dutasteride) at their index date or within 1 month of the induction period, they were excluded from the cohort. Otherwise, they entered the study cohorts based on their earliest record and were subsequently censored when they switched or used both drugs.

Outcome and covariates

The endpoint was the incidence of T2DM. Incidence of T2DM was defined as the first record of a primary or secondary diagnosis (ICD-10 code, E11) and/or receipt of oral diabetic agents (Supplementary Table 1, only online) for the first time. Data were censored when the patients presumably stopped using the drug (no new prescription for study drugs within the last day's supply plus the recorded number of days' supply plus a 180-day grace period to allow for dose adjustment and irregular use), when they switched to another treatment (e.g., tamsulosin to finasteride or tamsulosin to dutasteride) or from monotherapy to dual therapy, when they had a record of death, or at the end of the study period (December 31, 2020). This study considered the calendar year of the index date, age (modelled by cubic spline), national health insurance status, history of pre-diabetes (identified by ICD-10 code–R73.03), and comorbidities and medications (for the past 1 year prior to the index date) as covariates. The comorbidities and medications are as follows: comorbidities [chronic obstructive pulmonary disease (COPD), heart failure, hypertension, dyslipidemia] and medications [angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), beta blockers (BB), thiazide diuretics, statins, antidepressants, antipsychotics, and corticosteroids].

Statistical analysis

Main analysis

We carried out standardized mean difference (SMD) for baseline characteristics. A log-rank test was conducted to investigate the significance of difference in the probability of incidence of T2DM between cohorts during follow-up. A two-sided p-value<0.05 was deemed statistically significant. Kaplan–Meier curves were fitted in the unweighted population. Using a set of numerous covariates (age at the index date, insurer type at index, calendar year of the index date, history of pre-diabetes, ACEi, ARB, BB, thiazide, statin, corticosteroids, antidepressives, antipsychotics, COPD, heart failure, hypertensive disease, dyslipidemia), we predicted the propensity score (PS) for each patient in both cohorts. This set of covariates was chosen based on prior literature and clinical experience. To limit the influence of extreme weights on treatment comparison, we applied weight trimming at the 5th and 95th percentiles. We then created a pseudo-population with balanced covariates using stabilized inverse probability treatment weighting (SPITW).[16] After confirming that the maximum weight and the mean weights were 1.0 (for both cohorts), which limits the potential for influential patients to bias the results, we assessed the balance of observed covariates across treatment cohorts in the pseudo-population, with absolute SMD <0.1 deemed acceptable. Cox proportional hazards models were then fitted, without controlling for covariates, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Follow-up time for each patient was calculated as the time from the index date to the end of follow-up. The proportionality assumptions were mildly violated based on Schoenfeld proportionality tests for both cohorts (ρ=0.037, p=0.014 in the finasteride versus tamsulosin cohort; ρ=-0.058, p<0.01 in the dutasteride versus tamsulosin cohort). To address this mild violation, we conducted piecewise Cox models by follow-up intervals (0–2, 2–4, and 4–6 years). These cut points were based on visual inspection of KM curves, which indicated divergence between groups over time as well as clinically interpretable periods, and were confirmed by Schoenfeld's residual test, which indicated that the proportionality assumption was not violated within each model (Supplementary Table 2, only online). All statistical analyses were carried out using SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC, USA) and RStudio (RStudio Team, 2020) provided through the HIRA remote big data analysis system (https://ras.hira.or.kr/).

Sensitivity analysis

We conducted two sensitivity analyses to assess the robustness of our findings. First, to account for possible protopathic bias, we applied 1-year and 2-year lag time periods to the weighted populations in both cohorts and computed the adjusted HR using Cox proportional hazards models, without any additional adjustments. Considering that adherence might affect the outcomes, the cohort was stratified as higher adherence [≥70% medication possession ratio (MPR)] and lower adherence (<70% MPR). The MPR threshold was chosen due to its positive effect on BPH symptoms.[17] Subsequently, Cox proportional hazards model analyses were performed to estimate weighted HRs for each stratum. All sensitivity analyses used weighted populations created by SPITW without any additional adjustments.

RESULTS

Characteristics of the study cohort

A total of 34874 tamsulosin users and 16953 finasteride users were included in the tamsulosin-finasteride cohort (Table 1). Before weighting, finasteride users were more likely to use thiazide diuretics and statins and to have hypertension and heart failure compared with tamsulosin users. After weighting, all the baseline characteristics of finasteride and tamsulosin users became comparable. A total of 34874 tamsulosin users and 19480 dutasteride users were included in the tamsulosin-dutasteride cohort (Table 2). Before weighting, dutasteride users were less likely to use thiazide diuretics and corticosteroids and to have hypertension compared with tamsulosin users. After weighting, all baseline characteristics of dutasteride and tamsulosin users became comparable.

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Table 1. Baseline Characteristics of the Tamsulosin–Finasteride Cohort Before and After Application of Weighing

	Actual cohorts		SMD	Weighted cohorts*		SMD
	Tamsulosin (n=34874)	Finasteride (n=16953)		Tamsulosin (n=34872)	Finasteride (n=16955)	
Age (yr)	61.8±11.0	63.0±11.1	0.103	62.2±11.1	62.2±11.0	0.001
Health insurance	33706 (96.7)	16429 (96.9)	0.015	33734.6 (96.7)	16402.6 (96.7)	<0.001
Index year			0.155			0.002
2013	4483 (12.9)	2566 (15.1)		4740.0 (13.6)	2300.2 (13.6)	
2014	4225 (12.1)	2395 (14.1)		4449.3 (12.8)	2158.1 (12.7)	
2015	3922 (11.2)	2266 (13.4)		4160.5 (11.9)	2020.5 (11.9)	
2016	4367 (12.5)	1891 (11.2)		4211.3 (12.1)	2046.4 (12.1)	
2017	4333 (12.4)	1953 (11.5)		4231.7 (12.1)	2059.5 (12.1)	
2018	4621 (13.3)	2268 (13.4)		4637.7 (13.3)	2256.6 (13.3)	
2019	4899 (14.0)	2197 (13.0)		4778.1 (13.7)	2327.2 (13.7)	
2020	4024 (11.5)	1417 (8.4)		3663.6 (10.5)	1786.1 (10.5)	
History of pre-diabetes	8256 (23.7)	4062 (24.0)	0.007	8276.1 (23.7)	4006.9 (23.6)	0.002
ACEi	279 (0.8)	157 (0.9)	0.014	293.4 (0.8)	142.6 (0.8)	<0.001
ARB	6642 (19.0)	3331 (19.6)	0.015	6706.6 (19.2)	3256.7 (19.2)	0.001
BB	2078 (6.0)	1038 (6.1)	0.007	2095.2 (6.0)	1017.2 (6.0)	<0.001
Thiazide diuretics	2332 (6.7)	1241 (7.3)	0.025	2401.2 (6.9)	1165.8 (6.9)	<0.001
Statins	5320 (15.3)	2622 (15.5)	0.006	5340.9 (15.3)	2594.1 (15.3)	<0.001
Antidepressants and antipsychotics	824 (2.4)	404 (2.4)	0.001	824.7 (2.4)	397.4 (2.3)	0.001
Corticosteroids	1609 (4.6)	764 (4.5)	0.005	1592.7 (4.6)	767.2 (4.5)	0.002
COPD	818 (2.3)	426 (2.5)	0.011	837.3 (2.4)	407.9 (2.4)	<0.001
Heart failure	655 (1.9)	334 (2.0)	0.007	665.8 (1.9)	325.1 (1.9)	0.001
Hypertension	12278 (35.2)	6292 (37.1)	0.040	12490.3 (35.8)	6070.7 (35.8)	<0.001
Dyslipidemia	7064 (20.3)	3459 (20.4)	0.004	7081.0 (20.3)	3448.1 (20.3)	0.001

SMD, standardized mean difference; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; COPD, chronic obstructive pulmonary disease.
Values are expressed as mean±standard deviation or n (%).
*Weighted cohorts were created using stabilized inverse probability weighting with propensity scores obtained from multivariable logistic regression models incorporating baseline characteristics in Table 1 for each cohort.

Main analysis

Forest plots to summary analyses for both cohorts are presented in Figs. 1 and 2.

Finasteride–Tamsulosin cohort

During a mean follow-up of 2.9 years (SD 2.3), 2813 and 5063 patients with new-onset T2DM were identified in the finasteride and tamsulosin cohorts, respectively (Table 3). The unadjusted incidence of T2DM was 631 per 10000 person-years in finasteride users and 589 per 10000 person-years in tamsulosin users. Log-rank test indicated that the cumulative incidence rate of T2DM was higher (p=0.014) in finasteride users compared with tamsulosin users (Fig. 3). We found similar crude HR and adjusted HR of 1.06 (95% CI, 1.01–1.11). After stratification by follow-up time (to address the mild violation of the proportionality assumption), the adjusted risk in finasteride users fluctuated (ranging from 2% to 10%), with 95% CIs ranging from 0.90 to 1.33 (Table 4).

Dutasteride–Tamsulosin cohort

During a mean follow-up of 2.8 years (SD 2.3), 2550 and 5063 patients with new-onset T2DM were identified in the dutasteride and tamsulosin cohorts, respectively (Table 3). The unadjusted incidence of T2DM was 558 per 10000 person years in dutasteride users and 589 per 10000 person-years in tamsulosin users. Log-rank test indicated that the cumulative incidence rate of T2DM was not statistically different between dutasteride and tamsulosin users (p=0.480) (Fig. 4). We found similar crude HR and adjusted HR of 0.97 (95% CI, 0.92–1.02). After stratifying the results by follow-up time, the adjusted risk of developing T2DM decreased with longer follow-up times in dutasteride users (ranging from 1.00 to 0.87) compared with tamsulosin users (Table 4). The 95% CIs ranged from 0.71 to 1.08.

Sensitivity analysis

Overall, the results from the lag time analysis (Supplementary Table 3, only online) did not differ from those of the aggregate main analysis. The adjusted HRs for the finasteride–tamsulo-

Table 2. Baseline Characteristics of the Tamsulosin–Dutasteride Cohort Before and After Application of Weighting

	Actual cohorts		SMD	Weighted cohorts*		SMD
	Tamsulosin (n=34874)	Dutasteride (n=19480)		Tamsulosin (n=36570)	Dutasteride (n=17788)	
Age (yr)	61.8±11.0	61.9±12.1	0.009	61.9±11.4	62.0±11.4	0.008
Health insurance	33706 (96.7)	18925 (97.2)	0.029	35416.4 (96.8)	17235.6 (96.9)	0.003
Index year			0.299			0.003
2013	4483 (12.9)	1668 (8.6)		4143.0 (11.3)	2023.6 (11.4)	
2014	4225 (12.1)	1406 (7.2)		3793.1 (10.4)	1856.3 (10.4)	
2015	3922 (11.2)	1478 (7.6)		3632.3 (9.9)	1761.7 (9.9)	
2016	4367 (12.5)	3072 (15.8)		5007.4 (13.7)	2436.0 (13.7)	
2017	4333 (12.4)	3069 (15.8)		4981.8 (13.6)	2422.3 (13.6)	
2018	4621 (13.3)	3234 (16.6)		5280.4 (14.4)	2563.1 (14.4)	
2019	4899 (14.0)	3437 (17.6)		5601.4 (15.3)	2718.5 (15.3)	
2020	4024 (11.5)	2116 (10.9)		4130.7 (11.3)	2006.4 (11.3)	
History of pre-diabetes	8256 (23.7)	3977 (20.4)	0.079	8243.4 (22.5)	4026.6 (22.6)	0.002
ACEi	279 (0.8)	147 (0.8)	0.005	285.7 (0.8)	138.0 (0.8)	0.001
ARB	6642 (19.0)	3681 (18.9)	0.004	6956.9 (19.0)	3393.1 (19.1)	0.001
BB	2078 (6.0)	1031 (5.3)	0.029	2090.9 (5.7)	1012.0 (5.7)	0.001
Thiazide diuretics	2332 (6.7)	1248 (6.4)	0.011	2412.4 (6.6)	1175.6 (6.6)	<0.001
Statins	5320 (15.3)	3053 (15.7)	0.012	5641.2 (15.4)	2751.2 (15.5)	0.001
Antidepressants and antipsychotics	824 (2.4)	463 (2.4)	0.001	868.6 (2.4)	422.2 (2.4)	<0.001
Corticosteroids	1609 (4.6)	825 (4.2)	0.018	1635.6 (4.5)	793.9 (4.5)	<0.001
COPD	818 (2.3)	497 (2.6)	0.013	887.9 (2.4)	435.2 (2.4)	0.001
Heart failure	655 (1.9)	363 (1.9)	0.001	687.1 (1.9)	335.1 (1.9)	<0.001
Hypertension	12278 (35.2)	6466 (33.2)	0.042	12624.3 (34.5)	6153.4 (34.6)	0.002
Dyslipidemia	7064 (20.3)	3880 (19.9)	0.008	7386.4 (20.2)	3618.5 (20.3)	0.004

SMD, standardized mean difference; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; COPD, chronic obstructive pulmonary disease.
Values are expressed as mean±standard deviation or n (%).
*Weighted cohorts were created using stabilized inverse probability weighting with propensity scores obtained from multivariable logistic regression models incorporating baseline characteristics in Table 2 for each cohort.

sin cohort were 1.07 (95% CI, 1.01–1.12) for the 1-year lag and 1.10 (95% CI, 1.03–1.12) for the 2-year lag. Similarly, the adjusted HRs for the dutasteride–tamsulosin cohort were 0.97 (95% CI, 0.92–1.03) for the 1-year lag and 0.98 (95% CI, 0.92–1.03) for the 2-year lag. Among the study population with good compliance, a downward trend in adjusted HRs was observed in both cohorts: 1.01 (95% CI, 0.95–1.08) and 0.90 (95% CI, 0.86–0.97) for the finasteride–tamsulosin and dutasteride–tamsulosin cohorts, respectively (Supplementary Table 4, only online).

DISCUSSION

This is the first As-Treated (AT) protocol using national data to evaluate the risk of T2DM associated with 5-ARI use. We utilized the active comparator (tamsulosin) and SIPTW to minimize indication bias and confounding. Furthermore, the AT protocol, paired with the 3-year look-back period—the longest baseline ascertainment period reported in the literature on this subject—minimized prevalent-user bias and misclassification of exposure. In the main analysis, finasteride users had a slightly increased risk of T2DM compared with tamsulosin users (HR=1.06; 95% CI, 1.01–1.11), whereas the risk of T2DM did not significantly differ between dutasteride users and tamsulosin users. In the piecewise Cox analysis and when restricted to patients with good compliance, the risks did not exhibit statistical significance in either cohort.

A previous study demonstrated that BPH patients taking 5-ARIs have around an 18% higher likelihood of developing T2DM than those taking tamsulosin.[8] In this previous study, when comparing dutasteride and tamsulosin monotherapy groups matched by PS, dutasteride users had an adjusted HR of 1.34 (95% CI, 1.02–1.75) in the UK population and 1.18 (95% CI, 1.00–1.40) in the Taiwanese population. When comparing PS-matched finasteride and tamsulosin monotherapy groups, the adjusted risk of T2DM associated with finasteride use was 1.22-fold (95% CI, 0.95–1.57) and 1.61-fold (95% CI, 1.46–1.80) higher in the UK and Taiwanese data, respectively.[8] Their findings suggest that 5-ARI users may be at a higher risk of T2DM compared with tamsulosin users. Our results fall within

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the range of these CIs. In the present study using the South Korean database, we were able to utilize a larger number of records and apply SIPTW instead of PS matching to preserve our sample size, thereby improving the precision of the 95% CIs. Overall, our study yielded more conservative estimates with overlapping CIs compared with previous studies.[8,10] Method-

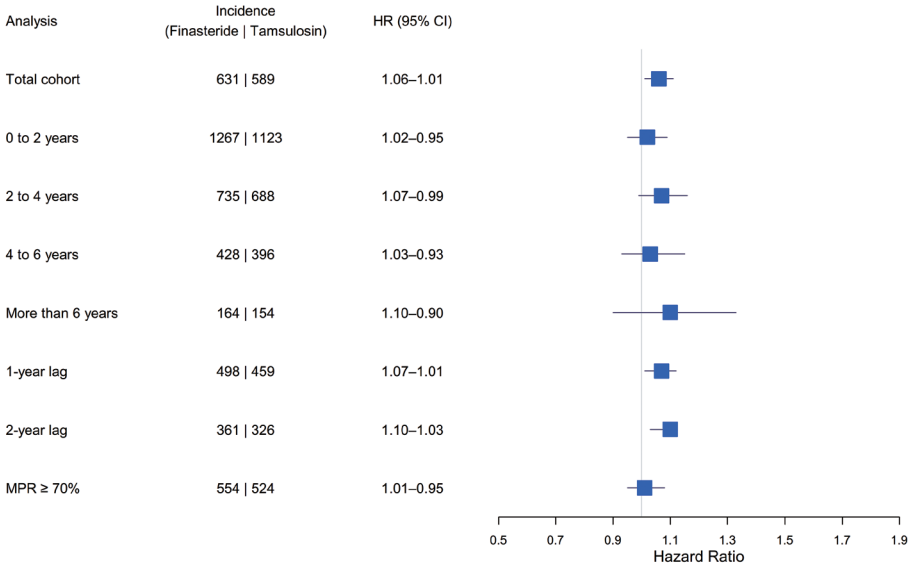

Fig. 1. Forest plot of estimates from Tamsulosin–Finasteride analyses. HR, hazard ratio; CI, confidence interval.

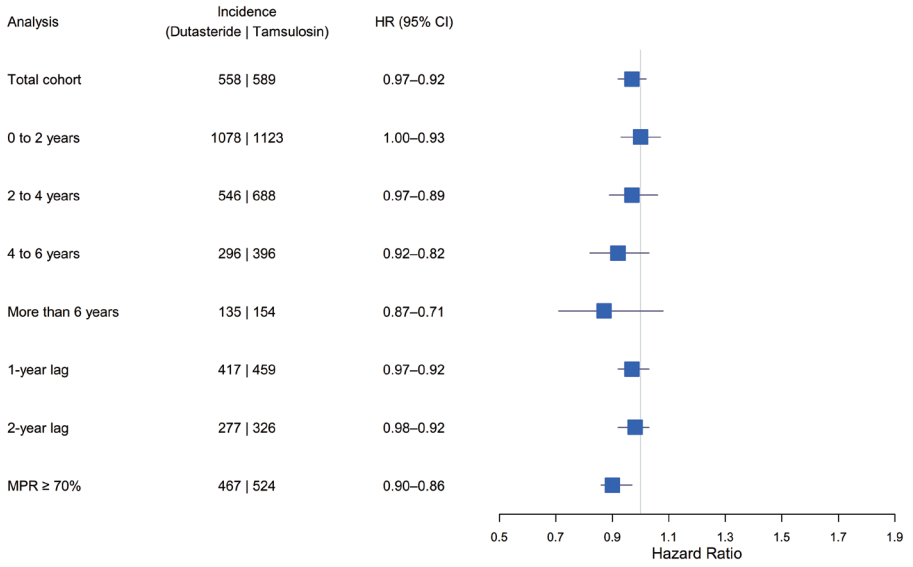

Fig. 2. Forest plot of estimates from Tamsulosin–Dutasteride analyses. HR, hazard ratio; CI, confidence interval.

Table 3. Risk of Type 2 Diabetes Mellitus in New Users of Finasteride and Dutasteride Compared with New Users of Tamsulosin

	n*	Events	Total person- years	Incidence (per 10000 person-years)	Crude HR	Adjusted HR†
Finasteride–Tamsulosin						
Finasteride	16953	2813	44579	631	1.06 (1.01–1.11)	1.06 (1.01–1.11)
Tamsulosin	34874	5063	85953	589	1.0 (reference)	1.0 (reference)
Dutasteride–Tamsulosin						
Dutasteride	19480	2550	45680	558	0.97 (0.92–1.01)	0.97 (0.92–1.02)
Tamsulosin	34874	5063	85953	589	1.0 (reference)	1.0 (reference)

HR, hazard ratio.
*Total number of patients in each cohort; †Using a weighted cohort created by stabilized inverse probability weighting without any additional adjustment.

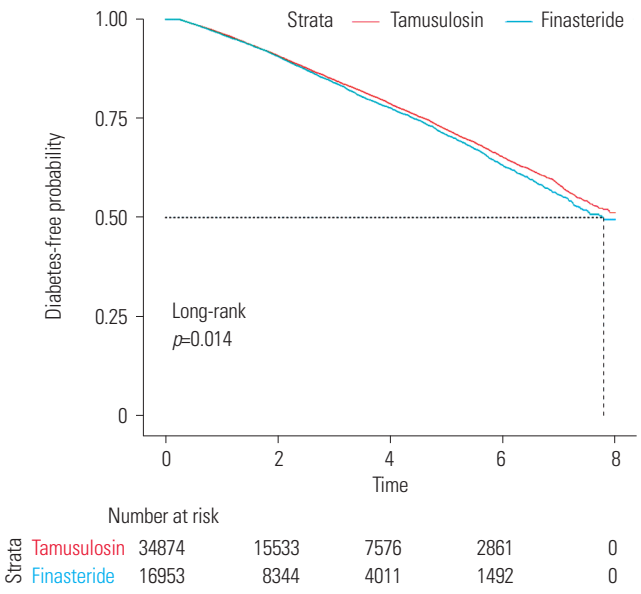

Fig. 3. Kaplan–Meier plot of Tamsulosin–Finasteride cohort.

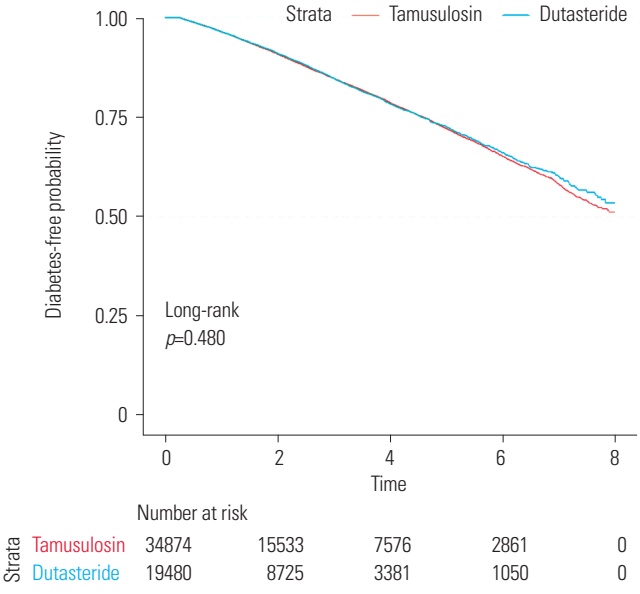

Fig. 4. Kaplan–Meier plot of Tamsulosin–Dutasteride cohort.

Table 4. Risk of Type 2 Diabetes Mellitus in New Users of Finasteride and Dutasteride Compared with New Users of Tamsulosin, Stratified by Survival Time

	n*	Events	Total person- years	Incidence (per 10000 person-years)	Crude HR	Adjusted HR†
<2 years						
Finasteride–Tamsulosin						
Finasteride	8609	1204	9504	1267	1.08 (1.01–1.16)	1.02 (0.95–1.09)
Tamsulosin	19341	2262	20149	1123	1.0 (reference)	1.0 (reference)
Dutasteride–Tamsulosin						
Dutasteride	10755	1283	11904	1078	0.90 (0.84–0.96)	1.00 (0.93–1.07)
Tamsulosin	19341	2262	20149	1123	1.0 (reference)	1.0 (reference)
2 to <4 years						
Finasteride–Tamsulosin						
Finasteride	4333	908	12351	735	1.14 (1.05–1.23)	1.07 (0.99–1.16)
Tamsulosin	7957	1583	22994	688	1.0 (reference)	1.0 (reference)
Dutasteride–Tamsulosin						
Dutasteride	5344	837	15321	546	0.82 (0.75–0.89)	0.97 (0.89–1.06)
Tamsulosin	7957	1583	22994	688	1.0 (reference)	1.0 (reference)
4 to <6 years						
Finasteride–Tamsulosin						
Finasteride	2519	533	12454	428	1.03 (0.93–1.15)	1.03 (0.93–1.15)
Tamsulosin	4715	914	23066	396	1.0 (reference)	1.0 (reference)
Dutasteride–Tamsulosin						
Dutasteride	2331	332	11207	296	0.86 (0.76–0.98)	0.92 (0.82–1.03)
Tamsulosin	4715	914	23066	396	1.0 (reference)	1.0 (reference)
≥6 years						
Finasteride–Tamsulosin						
Finasteride	1492	168	10271	164	1.08 (0.89–1.30)	1.10 (0.90–1.33)
Tamsulosin	2861	304	19744	154	1.0 (reference)	1.0 (reference)
Dutasteride–Tamsulosin						
Dutasteride	1050	98	7247	135	0.88 (0.70–1.10)	0.87 (0.71–1.08)
Tamsulosin	2861	304	19744	154	1.0 (reference)	1.0 (reference)

HR, hazard ratio.
*Total number of patients in each cohort; †Using a weighted cohort created by stabilized inverse probability weighting without any additional adjustment.

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ologically, similar to the previous study analyzing UK and Taiwanese data,[8] we utilized the active comparator (tamsulosin) and the PS method to minimize indication bias. Compared with previous studies,[8-10] the present study applied a stricter definition of drug exposure by censoring data at discontinuation of the drug of interest (defined as the last prescription day plus the duration of supply plus a 180-day grace period). Although this approach excluded patients who developed T2DM after discontinuation from being counted as drug-related events and might have underestimated T2DM incidence, it enabled us to avoid bias due to varying factors influencing T2DM risk after discontinuation of the drug of interest and to maximize the use of real-world data reflecting current clinical practice. This approach allows us to better utilize real-world data, reflecting clinical practice scenarios such as patients forgetting to fill prescriptions and pill cutting.

It is noteworthy that the risk of T2DM slightly increased in finasteride users but not in dutasteride users in the main analysis, although dutasteride is known to exert more profound systemic suppression of dihydrotestosterone through more potent inhibition of both type I and II 5α-reductase isoforms.[18] One possible explanation is lower hepatic expression of type I 5α-reductase activity and the resulting reduction in metabolic impact of dutasteride in East Asian populations.[19] In addition, pharmacokinetic differences between the drugs may play a role: dutasteride has a much longer half-life (up to 5 weeks) than finasteride (5–6 hours).[12,13] We speculate that more sustained suppression of 5α-reductase activity by dutasteride induces compensatory stabilization of glucose homeostasis. However, the potential impact of unmeasured confounders (e.g., genetic, lifestyle, and healthcare utilization factors) cannot be excluded, and neither finasteride nor dutasteride displayed significant associations with T2DM risk in our piecewise Cox analysis.

Clinically, given the minimal impact of 5-ARIs on the incidence of T2DM in our overall findings, there appears to be no compelling evidence to deter the use of 5-ARIs in BPH patients without underlying T2DM due to concerns about the risk of incident T2DM. Moreover, a recent population-based study demonstrated no significant risk of poor glycemic control associated with finasteride compared with tamsulosin use in T2DM patients.[20] Collectively, the use of 5-ARIs is unlikely to adversely affect glucose metabolism in either non-diabetic or diabetic patients, thereby supporting their safe use in clinical practice. However, it remains possible that specific patient subgroups may be susceptible to the diabetogenic effect of 5-ARIs. Particularly, traditional risk factors for T2DM (e.g., age, pre-diabetes, and cardiometabolic comorbidities) might modify the impact of 5-ARI use on the development of T2DM, which warrants future investigation. In addition, higher doses of 5-ARIs may be associated with an increased risk of T2DM. The present study did not evaluate dose–response relationships because both finasteride and dutasteride are prescribed at fixed doses in BPH treatment. Future studies may be needed to explore the dose–response relationship in male pattern hair loss, in which the treatment doses for finasteride and dutasteride vary.

Overall, this study demonstrated a modest to null effect of 5-ARIs on the risk of T2DM. However, it is necessary to interpret our results in the face of several limitations. First, we identified the incidence of T2DM based on diagnostic codes and prescriptions in routinely collected healthcare utilization data, although the same limitation applies to previous studies.[8-10] Second, given that T2DM patients develop hyperglycemia before diagnosis of T2DM and that hyperglycemia is associated with increased prostate size (the indication of 5-ARIs),[21] patients who first received finasteride might have potential protopathic bias. To address this potential bias, we conducted a sensitivity analysis applying lag times between drug prescription and the incidence of T2DM and found similar risk estimates to the main results. Third, although we had several thousand individuals with more than 6 years of follow-up (Table 4), the average follow-up time was approximately 3 years, which mirrored the duration of drug exposure because the data were censored when treatment was switched, stopped, or augmented. Thus, we cannot rule out the possibility of an increase in the risk of T2DM related to longer use of 5-ARIs. Fourth, our findings may not be generalizable to other countries with different ethnic compositions and healthcare systems. Fifth, our results may be affected by patients' compliance. We attempted to address this by conducting a sensitivity analysis on a subgroup of patients who had an MPR ≥70%. The results from this sensitivity analysis corroborated the minimal effects of 5-ARIs on the risk of T2DM, with the adjusted HRs for both finasteride and dutasteride showing a downward trajectory.

Due to the nature of the data source, there is a possibility of unmeasured confounders such as body mass index, smoking status, and alcohol consumption. In the previous study,[8] the UK data analysis adjusted for body mass index, smoking status, and alcohol consumption exhibited similar risk estimates to the Taiwanese data analysis that did not adjust for these factors. In addition, according to the American Urological Association, drug initiation may not depend on these factors.[22] Finally, a small number of patients who received insulin without oral hypoglycemic agents may have been included. Given the lack of oral therapy and potential etiologies other than T2DM, the inclusion of such individuals may have introduced potential misclassification bias.

In conclusion, this historical cohort study using nationwide primary-to-tertiary healthcare utilization data linked with prescription data found minimal effects of finasteride and dutasteride on the risk of T2DM compared with tamsulosin. This study may provide robust evidence regarding the risk of T2DM associated with the use of 5-ARIs among BPH patients.

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