Original Article
Prostate cancer

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Comparison of Finasteride and Dutasteride on Risk of Prostate Cancer in Patients with Benign Prostatic Hyperplasia: A Pooled Analysis of 15 Real-world Databases

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Purpose: Finasteride and dutasteride are used to treat benign prostatic hyperplasia (BPH) and reduce the risk of developing prostate cancer. Finasteride blocks only the type 2 form of 5-alpha-reductase, whereas dutasteride blocks both type 1 and 2 forms of the enzyme. Previous studies suggest the possibility that dutasteride may be superior to finasteride in preventing prostate cancer. We directly compared the effects of finasteride and dutasteride on the risk of prostate cancer in patients with BPH using a pooled analysis of 15 real-world databases.

Materials and Methods: We conducted a multicenter, cohort study of new-users of finasteride and dutasteride. We include patients who were prescribed 5 mg finasteride or dutasteride for the first time to treat BPH and had at least 180 days of prescription. We excluded patients with a history of prostate cancer or a prostate-specific antigen level ≥ 4 ng/mL before the study drug prescription. Cox regression analysis was performed to examine the hazard ratio (HR) for prostate cancer after propensity score (PS) matching.

Results: A total of 8,284 patients of new-users of finasteride and 8,670 patients of new-users of dutasteride were included across the 15 databases. In the overall population, compared to dutasteride, finasteride was associated with a lower risk of prostate cancer in both on-treatment and intent-to-treat time-at-risk periods. After 1:1 PS matching, 4,897 patients using finasteride and 4,897 patients using dutasteride were enrolled in the present study. No significant differences were observed for risk of prostate cancer between finasteride and dutasteride both on-treatment (HR=0.66, 95% confidence interval [CI]: 0.44–1.00; p=0.051) and intent-to-treat time-at-risk periods (HR=0.87, 95% CI: 0.67–1.14; p=0.310).

Conclusions: Using real-world databases, the present study demonstrated that dutasteride was not associated with a lower risk of prostate cancer than finasteride in patients with BPH.

Keywords: Dutasteride; Finasteride; Prostatic hyperplasia; Prostatic neoplasms

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INTRODUCTION

Prostate cancer ranks as the second most diagnosed malignancy in men and is a major contributor to cancer-related deaths [1]. Finasteride and dutasteride are utilized for treating benign prostatic hyperplasia (BPH), and notably, they have shown effectiveness in lowering the risk of prostate cancer development [2,3]. Both drugs are 5-alpha-reductase inhibitors (5-ARIs) and act to inhibit the conversion of testosterone to dihydrotestosterone (DHT), which is involved in the development and progression of prostate cancer [4]. Finasteride selectively inhibits the type 2 form of 5-alpha-reductase, while dutasteride inhibits both type 1 and 2 forms of the enzyme [5,6]. By inhibiting both types of 5-alpha-reductases, several studies demonstrated that dutasteride may be more effective than finasteride at reducing DHT levels and prostate volume, and improving BPH symptoms [7,8]. In addition, the subgroup analysis results of a recent meta-analysis revealed that dutasteride users were at a lower risk of overall prostate cancer compared to non-users in three randomized clinical trials (RCTs), while finasteride users did not have a low risk of prostate cancer in eight RCTs [9]. However, insufficient studies are available that direct compare the effects of finasteride and dutasteride on the risk of prostate cancer.

In the present new-user model cohort study, we directly compared the effects of finasteride and dutasteride on the risk of prostate cancer in patients with BPH and without high prostate-specific antigen (PSA) levels using the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) version of big data, a framework that has been validated in our previous research endeavors [10,11].

MATERIALS AND METHODS

1. Data sources

We implemented a user-active comparator cohort design, utilizing real-world clinical big data. The dataset comprised a total of 17,921,657 patients from 15 hospitals in Korea, and the information was transformed into the OMOP-CDM version 5.3: (1) Kangdong Sacred Heart Hospital CDM (KDH, 1,209,068 patients); (2) Keimyung University Daegu Dongsan Medical Center CDM (DSMC, 491,805 patients); (3) Daegu Catholic University Medical Center CDM (DCMC, 949,936 patients); (4) Wonkwang University Hospital CDM (WKUH, 904,774 patients); (5) Myongji Hospital CDM (MJH, 1,039,519 patients); (6) Ewha Womans University Medical Center CDM (EUMC, 1,816,808 patients); (7) Pusan National University Hospital (PNUH, 1,753,001 patients); (8) Gyeongsang National University Hospital CDM (GNUH, 650,525 patients); (9) Soonchunhyang University Seoul Hospital CDM (SCHSU, 1,094,041 patients); (10) Soonchunhyang University Gumi Hospital CDM (SCHGM, 632,252 patients); (11) Soonchunhyang University Bucheon Hospital CDM (SCHBC, 1,325,214 patients); (12) Soonchunhyang University Cheonan Hospital CDM (SCHCA, 987,701 patients); (13) Kyung Hee University Hospital Gang Dong CDM (KHNMC, 880,275 patients); (14) Kyung Hee Medical Center CDM (KHMC, 1,222,935 patients); (15) Ajou University Medical Center CDM (AUMC, 2,959,803 patients). Each database contains de-identified patient-level electronic medical record (EMR) data that underwent conversion into the standard vocabulary of the CDM [12,13].

2. Ethics statement

This study received approval from the Institutional Review Board (IRB) of Kangdong Sacred Heart Hospital (IRB number 2022-12-011). The other 14 hospitals participating are affiliated with the Research Border Free Zone of the Korea CDM data network, which acknowledges the IRB approval from the research organizing center and exempts individual IRB approval. Written informed consent was waived by the IRB, and the research adhered to the principles outlined in the Declaration of Helsinki.

3. Study design

We conducted a multicenter cohort study of new users of finasteride and dutasteride. The target cohort comprised patients who were prescribed 5 mg finasteride for the first time for BPH treatment. As previous studies indicating an enhanced preventive effect with prolong use of 5-ARIs, we only enrolled patients who had at least 180 days of prescription [14,15]. The comparator cohort comprised patients who were prescribed 0.5 mg dutasteride for the first time for BPH treatment and had at least 180 days of prescription. Continuous drug exposure was defined by permitting intervals of less than 90 days between prescriptions. To ensure consistency in defining "new users" and mitigate immortal-time bias, we included only patients

with a continuous observational period more than 365 days before the initial prescription day of the study drugs. Furthermore, we included only patients who were diagnosed with BPH or prescribed alpha-blocker treatment within 365 days before and 180 days after the cohort start date. Patients meeting any of the following criteria were excluded from the study cohort: (1) having a PSA level ≥4 ng/mL within 365 days before and 180 days after the cohort start date; (2) a diagnosis of prostate cancer any day before as well as within 180 days after the cohort start date; and (3) a history of exposure to both finasteride and dutasteride. The cohort start date was defined as the initial prescription date of the study drug, while the cohort end date was defined as the cessation date of drug use.

The primary outcome was the diagnosis of prostate cancer 180 days after the cohort start date. Prostate cancer was identified using diagnostic codes of SNOMED CT (code 93974995, primary malignant neoplasm of prostate; code 399068003 malignant tumor of prostate; code 254900004 carcinoma of prostate) converted from code of 10th revision of the International Statistical Classification of Diseases (C61 Malignant neoplasm of prostate) in OMOP-CDM. The secondary outcome was the PSA level ≥4 ng/mL 180 days after the cohort start date. The present study examined two time-at-risk periods: (1) the on-treatment period, focused on evaluating the risk during exposure to the study drug, which was defined as the time from 180 days after the cohort start date until 180 days after the cohort end date, and (2) the intention-to-treat period, focused on evaluating the risk after exposure to the study drug, which was defined as the time from 180 days after the cohort start date until the patient's observation end.

4. Statistical analysis

We performed our cohort study using the open-source Observational Health Data Sciences and Informatics Cohort Method R package, complemented by large-scale analytics facilitated by the Cyclops R package [16]. We employed ATLAS version 2.7.5 for our study, and the analysis was conducted utilizing FEEDER-NET, a Korean health data platform built on the OMOP-CDM. To mitigate potential confounding factors arising from baseline covariate imbalances, we implemented large-scale propensity score (PS) matching to ensure balance between the target and comparator cohorts. The covariates utilized in the PS model consisted of age, medical history, and the prescription of medications within 30 days and 365 days prior to the cohort start date. Additionally, the prescription period of the study drugs was also taken into consideration in the PS model. PSs were calculated through a large-scale logistic regression model, and greedy search matching was applied to match patients with a caliper of 0.2 times for the standard deviation of the PS distribution. In each of the 15 databases, we conducted 1:1 PS matching to compare finasteride and dutasteride. After conducting an identical analytical process on 15 databases with the single execute-to-end dedicated R package, we aggregated the results of baseline covariates, cohort start and end dates, observation end dates, outcome occurrence, and outcome-free survival time before and after PS matching according to the treatment groups from 15 databases. We then performed a pooled analysis to compare the finasteride and dutasteride. Kaplan-Meier analysis was employed to estimate the cumulative hazard ratio (HR) for prostate cancer. Additionally, a Cox regression analysis was conducted to examine the HR and 95% confidence intervals (CIs) for prostate cancer. Incidence rates were calculated as cases of prostate cancer per 1,000 person-years, obtained by dividing the number of cases by the total person-years at risk. Statistical significance was determined by 2-sided p-values, with values <0.05 considered as statistically significant. The analyses were carried out using the R Statistical software version 3.6.1 (R Foundation for Statistical Computing).

RESULTS

1. Study population

In the study, a total of 16,954 patients meeting the inclusion criteria were included across 15 databases (8,284 patients were new users of finasteride [46,795 person-years of follow-up] and 8,670 patients were new users of dutasteride [41,798 person-years of follow-up]) (Fig. 1). We performed 1:1 PS matching to compare the finasteride and dutasteride groups in each of 15 databases. From 4,059 (DSMC) to 8,460 (AUMC) baseline covariates were used for matching (Supplement Fig. 1). In total, 4,897 patients treated with finasteride and 4,897 patients treated with dutasteride were pooled from 15 databases after 1:1 PS matching (Supplement Table 1). Table 1 shows the major baseline characteristics of

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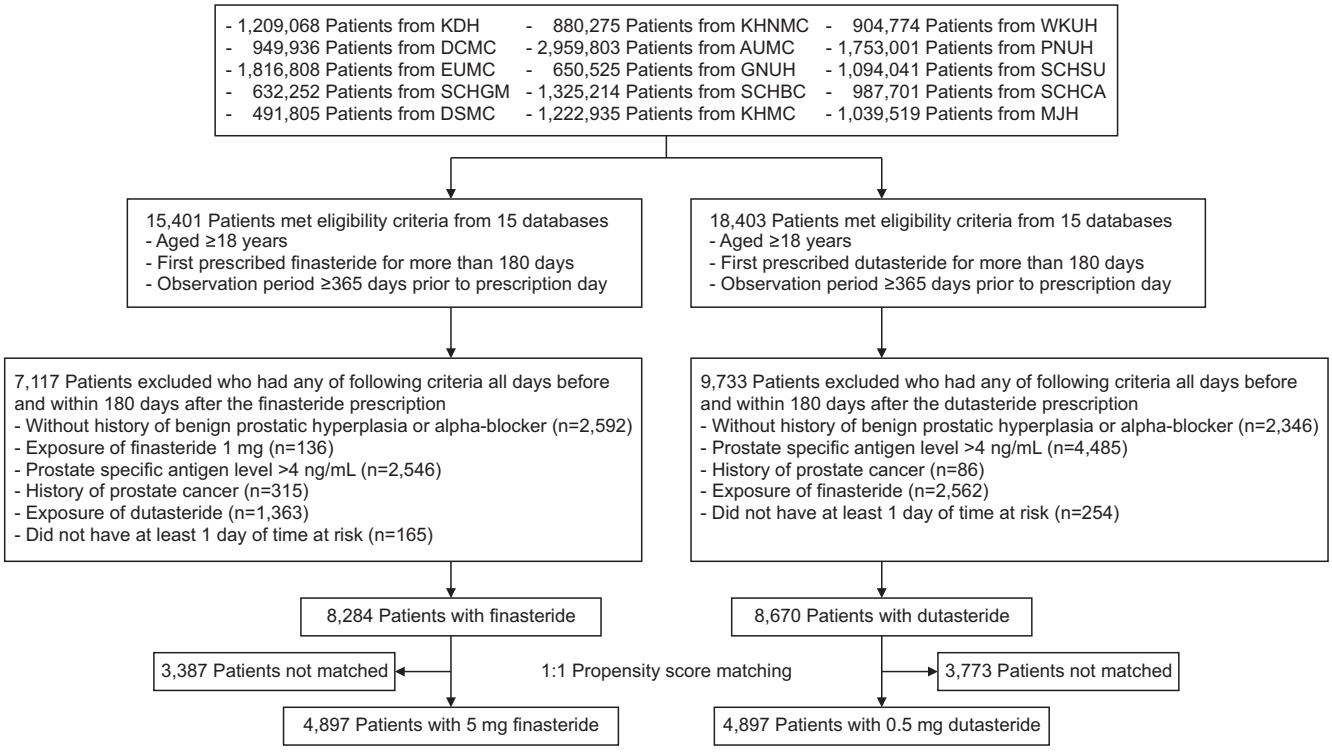

Fig. 1. Study flowchart of patients treated with finasteride *versus* those treated with dutasteride.

patients in both cohorts before and after PS matching. About 92% of patients had a diagnosis of BPH and 81% were taking alpha-blockers. The other baseline covariates were also well-balanced after PS matching.

2. Risk of prostate cancer between finasteride and dutasteride

In the overall population before PS matching, the incidence rate of prostate cancer was 3.37 cases/1,000 person-years during a median prescription period of 685 days (interquartile range [IQR], 468–1,187 days) in the finasteride cohort and 5.42 cases/1,000 person-years during median 709 days (IQR, 473–1,227 days) in the dutasteride cohort. Finasteride was associated with lower risk of prostate cancer compared to dutasteride in on-treatment time-at-risk analysis (HR=0.45, 95% CI: 0.33–0.63; p<0.001) (Fig. 2A). However, no statistically significant difference was observed between the two cohorts after PS matching (HR=0.66, 95% CI: 0.44–1.00; p=0.051) (Fig. 2B). In the intent-to-treat time-at-risk analysis, the incidence rate of prostate cancer was 3.70 cases / 1,000 person-years during a median observation period of 1,794 days (IQR, 846–3,118 days) in the finasteride cohort and 5.89 cases/1,000 person-years during median 1,506 days (IQR, 719–2,800 days) in the dutasteride cohort. Although the incidence of prostate cancer was significantly lower in the finasteride cohort compared to the dutasteride cohort before PS matching (HR=0.62, 95% CI: 0.51–0.76; p<0.001), no significant difference was detected between the two cohorts after PS matching (HR=0.87, 95% CI: 0.67–1.14; p=0.310) (Fig. 3).

3. Risk of the prostate-specific antigen level >4 ng/mL between finasteride and dutasteride

In the on-treatment analysis after PS matching, incidence rate of PSA level >4 ng/mL was 10.26/1,000 person-years in finasteride cohort and 11.04/1,000 person-years in dutasteride cohort, and no significant difference was observed between both cohorts (HR=0.90, 95% CI: 0.65–1.25; p=0.532) (Fig. 4A). Intent-to-treat analysis also demonstrated no significant differences in incidence of PSA level >4 ng/mL between both cohorts after PS matching (HR=0.97, 95% CI: 0.82–1.14; p=0.675) (Fig. 4B).

DISCUSSION

In this large pooled-analysis of real-world CDM data from 15 institutions, finasteride was associated with

Table 1. Baseline characteristics of study participants

	Before matching[a]			After matching		
	Finasteride (n=8,284)	Dutasteride (n=8,670)	Std. diff	Finasteride (n=4,897)	Dutasteride (n=4,897)	Std. diff
Age group (y)[b]						
40–44	0.38	0.77	-0.05	0.49	0.45	0.01
45–49	0.9	1.58	-0.06	1	0.98	0
50–54	2.58	3.14	-0.03	2.85	2.65	0.01
55–59	5.43	5.5	0	5.49	5.51	0
60–64	8.4	7.98	0.02	8.62	8.44	0.01
65–69	9.18	9.17	0	9.65	9.22	0.01
70–74	9.57	8.67	0.03	9.38	9.82	-0.01
75–79	7.39	6.73	0.03	6.89	6.87	0
80–84	4.03	3.68	0.02	3.85	3.84	0
Hypertension	12.46	10.57	0.06	12.04	12.61	-0.02
Diabetes mellitus	6.14	5.44	0.03	5.88	6.22	-0.01
Stroke	1.4	1.26	0.01	1.49	1.3	0.02
Heart failure	1.39	1.07	0.03	1.26	1.33	-0.01
Renal impairment	2.87	2.54	0.02	2.66	2.75	-0.01
Benign prostatic hyperplasia	87	87.7	-0.01	91.96	91.96	0
Urinary tract infection	2.76	2.28	0.03	2.59	2.57	0
Ureteric stone	1.86	2.28	-0.03	1.98	2.13	-0.01
Urinary tract obstruction	5.4	5.53	-0.01	6.13	6.27	-0.01
Neurogenic bladder	4.53	4.65	-0.01	4.68	4.89	-0.01
Hematuria	3.58	3.57	0	3.61	3.8	-0.01
Alpha-blocker	81.91	78.22	0.08	80.82	81.37	-0.01
Renin-angiotensin blocker	12.27	10.35	0.06	11.58	11.67	0
Beta-blocker	6.25	6.13	0.01	5.96	6.13	-0.01
Calcium channel blocker	21.08	19.8	0.03	16.58	19.90	-0.08
Statin	12.07	11.02	0.03	12.02	12.3	-0.01

Std. diff: standard difference of the mean.
[a]Data are presented as a percentage of the sample size. [b]Age groups younger than 40 years or older than 85 years were omitted.

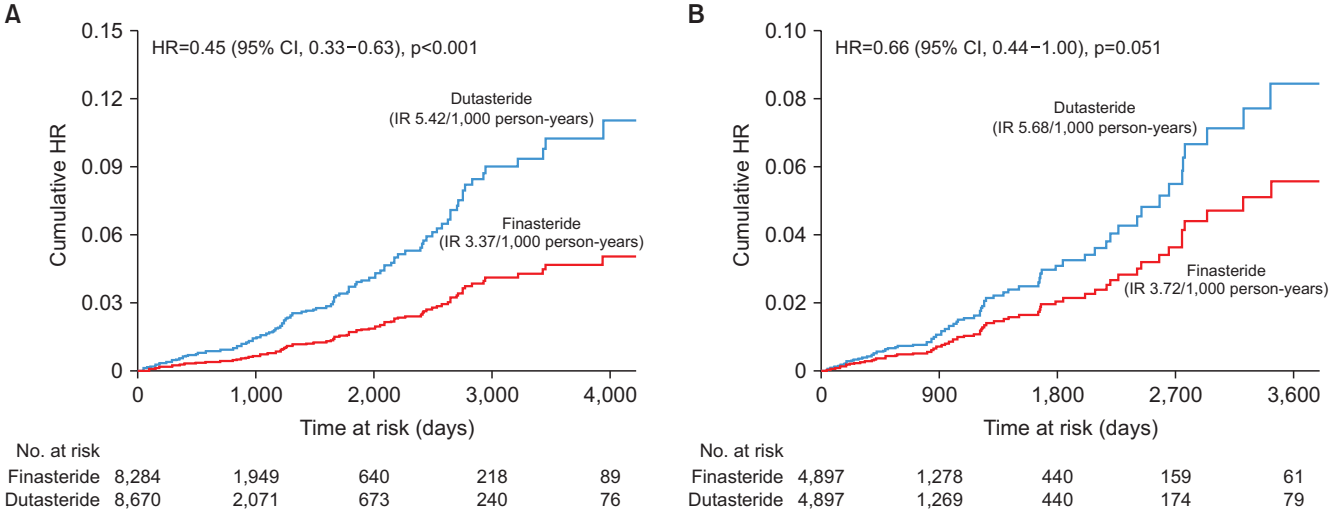

Fig. 2. Cumulative hazard ratios for prostate cancer between finasteride and dutasteride in on-treatment time-at-risk analysis. (A) In the overall population before propensity score matching, (B) after 1:1 propensity score matching. HR: hazard ratio, CI: confidence interval, IR: incidence rate is determined as the number of cases per 1,000 person-years.

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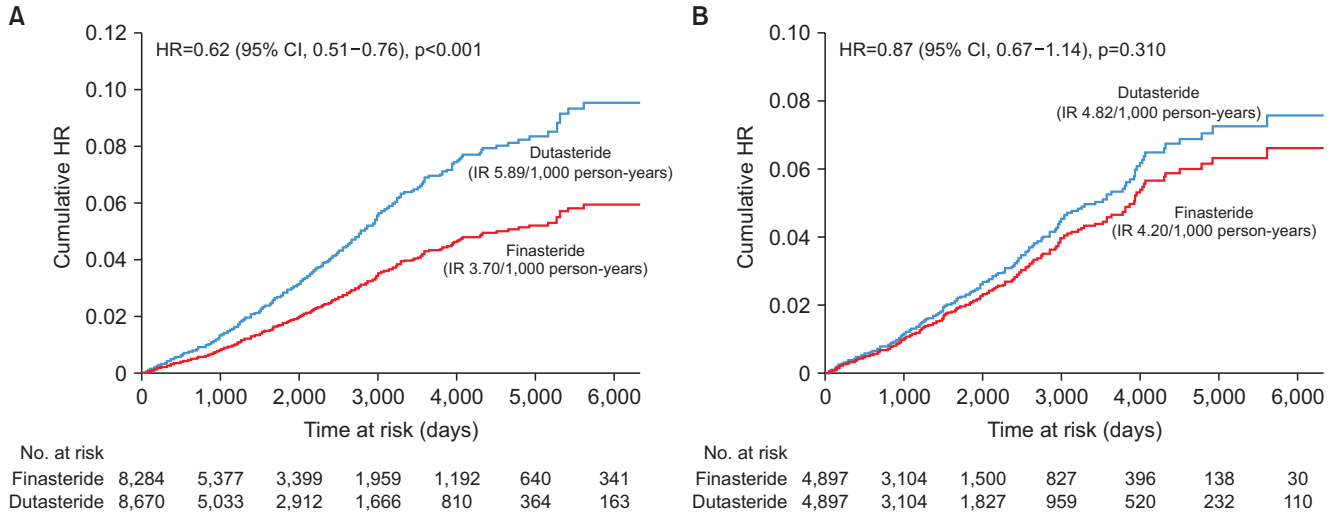

Fig. 3. Cumulative hazard ratios for prostate cancer between finasteride and dutasteride in intent-to-treat time-at-risk analysis. (A) In the overall population before propensity score matching, (B) after 1:1 propensity score matching. HR: hazard ratio, CI: confidence interval, IR: incidence rate is determined as the number of cases per 1,000 person-years.

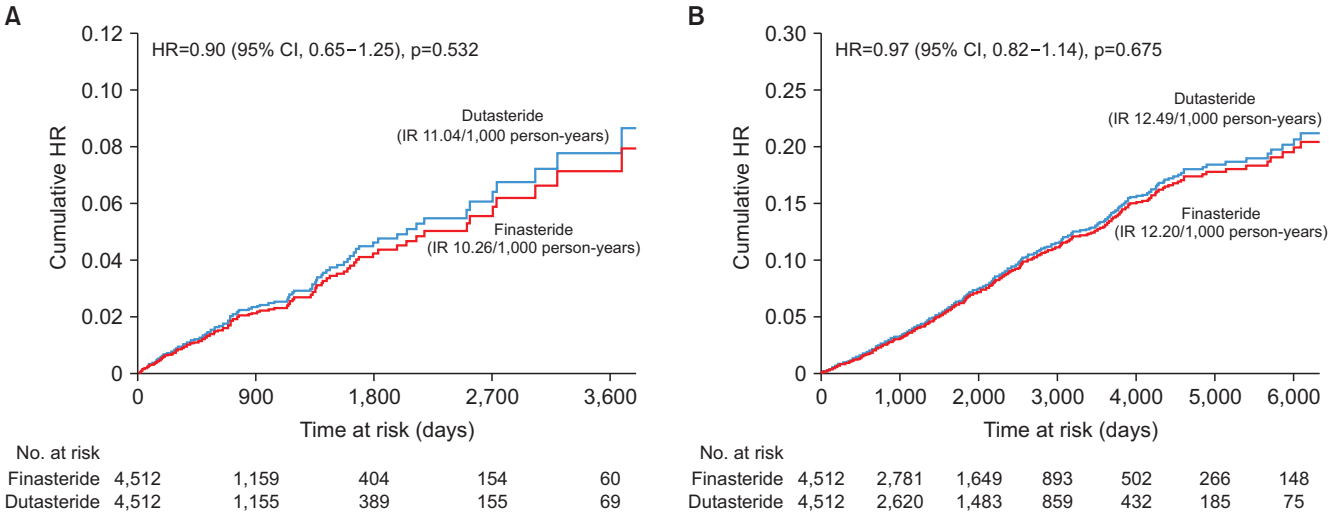

Fig. 4. Cumulative hazard ratios for prostate-specific antigen level ≥4 ng/mL between finasteride and dutasteride after propensity score matching. (A) On-treatment time-at-risk analysis , (B) intent-to-treat time-at-risk analysis. HR: hazard ratio, CI: confidence interval, IR: incidence rate is determined as the number of cases per 1,000 person-years.

a lower risk of overall prostate cancer than dutasteride during the period of exposure to 5-ARI and until the end of the patient's observation period. However, these results were not statistically significant after PS matching. In addition, the incidence of PSA level ≥4 ng/mL also did not differ in both treatment cohorts after PS matching. The present study hypothesized that dutasteride might be more effective than finasteride in preventing prostate cancer; however, this was not confirmed.

Previous studies demonstrated that 5-ARIs reduced risk of overall prostate cancer (summarized at Supplement Table 2). In addition, there were studies about dutasteride is more effective than finasteride in reducing DHT levels and prostate volume [4,7,8]. A study using prostate cancer specimens revealed an elevation in the expression of type 1 5-alpha-reductase and a reduction in the expression of type 2 5-alpha-reductase in prostate cancer specimens [17]. Another study demonstrated that type 1 5-alpha-reductase expression was three to four times higher in cancer-affected prostate tissue than in normal prostate tissue, whereas type 2 5-alpha-reductase expression was similar in both specimens [18]. These results suggest the possibility that

dutasteride might be more superior to finasteride in preventing prostate cancer. However, a lack of studies exists that directly compare these two drugs. As far as our knowledge extends, this study represents the initial attempt to directly compare the two drugs. The active-comparator and new-user design employed in the present study serves to alleviate the methodological limitations often associated with retrospective studies. Additionally, the implementation of large-scale PS matching helps mitigates the potential for confounding bias. In analyses conducted on all patients before PS matching, a low incidence of prostate cancer was observed in the finasteride group during both the on-treatment and intent-to-treat time-at-risk periods. As the results were not statistically significant after PS matching, this should not be overestimated. Nevertheless, when considering the p-value, a possibility exists that the reduced sample size after PS matching might have led to a loss of statistical significance. However, because previous studies have favored dutasteride over finasteride in terms of DHT levels, prostate volume, and rate of progression of prostate cancer, providing a rationale for our null finding is difficult [19]. One possible explanation is that, even though there are differences in activity between finasteride and dutasteride, prolonged and cumulative use for a certain period might lead to the effects reaching a plateau in terms of prostate volume reduction and in its potential for preventing prostate cancer. Previous RCT demonstrated no difference in prostate volume change between finasteride and dutasteride after 1-year treatment [20]. Since we enrolled patients who had taken the medications at least 180 days, there is a possibility of relevance to the results. Another possible explanation is that even though we do not have information about prostate volume or severity of lower urinary tract symptoms, dutasteride might have been used more in high-risk patients with large prostate volumes or severe symptoms due to the higher potency of the drug as a 5-ARI before PS matching. Although we used medical history and drugs as covariates in PS matching, it is possible that the risk factors for prostate cancer were distributed similarly across both cohorts because the large-scale PS matching decreased confounding bias. This may be the reason for the lack of significant differences after PS matching.

Due to the inherent significant bias introduced in the observational study when comparing active treatment with a placebo, we did not investigate whether 5-ARI reduced the risk of prostate cancer in users compared to non-users [21]. The present study included patients diagnosed with BPH or those taking an alpha-blocker for lower urinary symptoms and a normal PSA level, which is the setting most consistent with routine clinical practice. The significance of the present study is that, in patients receiving 5-ARI therapy, dutasteride is not more effective than finasteride in reducing the risk of prostate cancer. We lacked data on the changes in prostate volume after 5-ARI treatment, which is negatively associated with prostate cancer. To overcome this limitation, we evaluated PSA levels of >4 ng/mL as one of the study outcomes. Furthermore, PSA level is a critical variable in assessing the risk of prostate cancer with 5-ARIs. We excluded patients with PSA levels exceeding 4 ng/mL before starting 5-ARIs to control for confounding effects of PSA levels. We indirectly assessed potential cancer risk using PSA and identified no statistically significant difference between the two drugs.

A recent meta-analysis suggested that finasteride should be administered for at least 4 years to prevent prostate cancer [9]. In addition, registry data demonstrated the reducing in the risk of prostate cancer after 5-ARIs was pronounced with long treatment duration (0.1–2.0 years, HR=0.81 *vs.* 6–8 years, HR=0.31) [15]. In the present study, the median prescription duration was 495 days (IQR, 288–992 days) for finasteride and 499 days (IQR, 284–1,000 days) for dutasteride after PS matching, which may have been a relatively short treatment period for assessing the risk of prostate cancer. Nevertheless, Unger et al. demonstrated that the protective effects of finasteride endured even after discontinuation of the drug and extended after the median follow-up duration of up to 16 years [22]. Therefore, we assessed the risk of prostate cancer not only during the period of exposure to 5-ARIs, but also until the end of the observation period. During both time-at-risk periods, finasteride was possibly considered a safe option with regard to the risk of prostate cancer, although the result was not statistically significant after PS matching.

Our study has some limitations. First, our analysis was based on observational data, which implies that the possibility of confounding factors cannot be completely ruled out. For instance, family history of prostate cancer is known to be associated with pros-

tate cancer incidence [23], but the relevant information was unavailable because the family history had not been converted into the CDM. Moreover, because information on prostate cancer was identified using the diagnosis code in the EMR data at each hospital, patients diagnosed in hospitals not encompassed in the study might not have been captured. Second, we included only patients diagnosed with BPH or those concurrently taking alpha-blockers and 5-ARIs, however, there is a possibility that patients taking 5-ARIs for the treatment of androgenic alopecia might be included in present study. Third, our study was limited to East Asian men with BPH; therefore, our findings may not be generalizable to other populations. Previous studies have demonstrated that the incidence of prostate cancer in Asians is much lower than that in the Western population [24], it is important to be cautious about extending these findings to other ethnicities. Fourth, previous studies have displayed the possibility that 5-ARI increased the risk of high-grade prostate cancer [9]. However, we did not have data on Gleason Scores for prostate cancer; therefore, we could not compare the risk of high-grade prostate cancer. Lastly, the present study did not analyze the side effects of 5-ARI drug use or cautionary information; therefore, further research is needed in these areas.

CONCLUSIONS

The present study demonstrated that dutasteride was not associated with a lower risk of prostate cancer compared to finasteride during both drug exposure and at the end of the patient observation period after PS matching. Although the risk of overall prostate cancer was lower in the finasteride cohort than in the dutasteride cohort before PS matching, it should not be overinterpreted. Our study contributes to the growing body of evidence supporting the safety of finasteride and dutasteride concerning the risk of prostate cancer.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: DYY, WWS, RWP. Data curation: all authors. Formal analysis: DYY, WWS. Investigation: DYY, WWS, JMC, YSH. Methodology: RWP, SYR, CWJ, KJK. Project administration: DYY, WWS. Resources: all authors. Software: DYY, WWS, RWP. Supervision: DYY, SYR, HJY. Validation: WWS, PRW, YSH, DKK. Visualization: WWS, KJK. Writing – original draft: DYY, WWS. Writing – review & editing: all authors.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.5534/wjmh.230327.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/WLPHKF.

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