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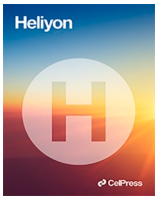

Research article

# Risk of poor glycemic control in tamsulosin versus finasteride users with type 2 diabetes mellitus

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ABSTRACT

*Background:* Benign prostatic hyperplasia (BPH) is strongly related to type 2 diabetes. Recent evidence has been inconsistent regarding the effect of BPH medications on glucose homeostasis. This study examined the risk of poor glycemic control associated with finasteride and tamsulosin use in individuals with type 2 diabetes.

*Methods:* We conducted a retrospective cohort study with a new-user, active-comparator design, utilizing nationwide pharmaceutical dispensing and hospitalization databases in New Zealand. The study cohort consisted of men with type 2 diabetes who were prescribed finasteride (n = 1,259) or tamsulosin (n = 580). Inverse probability treatment weighting using propensity scores was applied to create a weighted population with balanced baseline covariates. Cox proportional hazard models were fitted to estimate the risk.

*Results:* During a median follow-up of 2.4 years for finasteride users and 1.6 years for tamsulosin users, the incidence rates were 564 per 10,000 person-years and 409 per 10,000 person-years in tamsulosin users and finasteride users, respectively. After applying inverse probability treatment weighting, tamsulosin users did not have a significantly higher risk of poor glycemic control compared with finasteride users (weighted hazard ratio 1.27, 95 % confidence interval 0.95–1.72). Sensitivity analyses addressing confounding and protopathic bias yielded similar risk estimates.

*Conclusions:* We found that there was a non-differential risk of poor glycemic control between tamsulosin users and finasteride users during long-term use.

## 1. Introduction

Benign prostatic hyperplasia (BPH) is one of the most common urological conditions affecting men. The global prevalence of BPH increased from 51.1 million cases in 2000 to 94 million cases in 2019. Furthermore, the burden of BPH is projected to increase [1], emphasizing the need for an effective management strategy for this condition. Recent studies have shown an association of prostate enlargement with elevated fasting plasma glucose and insulin levels [2,3], which may be explained by biological mechanisms such as sex steroid metabolism, systemic inflammation, and insulin-like growth factor activity [4]. Two large, high-quality studies [5,6] and a meta-analysis [7] have linked hyperglycemia to more severe lower urinary tract symptoms in patients with BPH. Given the link

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between prostate enlargement and glucose metabolism, glycemic status is a critical factor to consider in the management of BPH.

Studies have investigated the effect of BPH medications on glucose metabolism; however, their findings are mixed. An animal study found that 5-alpha reductase inhibitors (5-ARis) influenced glucocorticoid metabolism by reducing the levels of androgen dihydrotestosterone, consequently inducing steatotic liver disease and hepatic insulin resistance [8]. Similar effects have also been observed in humans. For example, a meta-analysis reported an association between androgen deprivation therapy and an increased risk of diabetes mellitus [9]. A randomized controlled trial involving 46 BPH patients reported decreased hepatic insulin sensitivity among patients treated with dutasteride, a 5-ARi [10]. Similarly, mixed findings have been observed in studies examining the alpha-blocker drug class. A single-arm clinical trial found favorable effects of doxazosin, a non-specific alpha-blocker, on glycemic control in hypertensive patients with type 2 diabetes mellitus (T2DM) [11]. Conversely, a recent case series suggested that tamsulosin, a uroselective alpha-blocker, may induce hyperglycemia in patients with T2DM [12,13]. These inconsistent findings underscore the need for further investigation through large-scale pharmaco-epidemiological studies. Two such studies have been published, though they produced conflicting results despite using similar databases [14,15]. Both studies compared the risk of developing T2DM in BPH patients who took 5-ARis versus those who did not. The earlier study, which drew data from the National Health Insurance Research

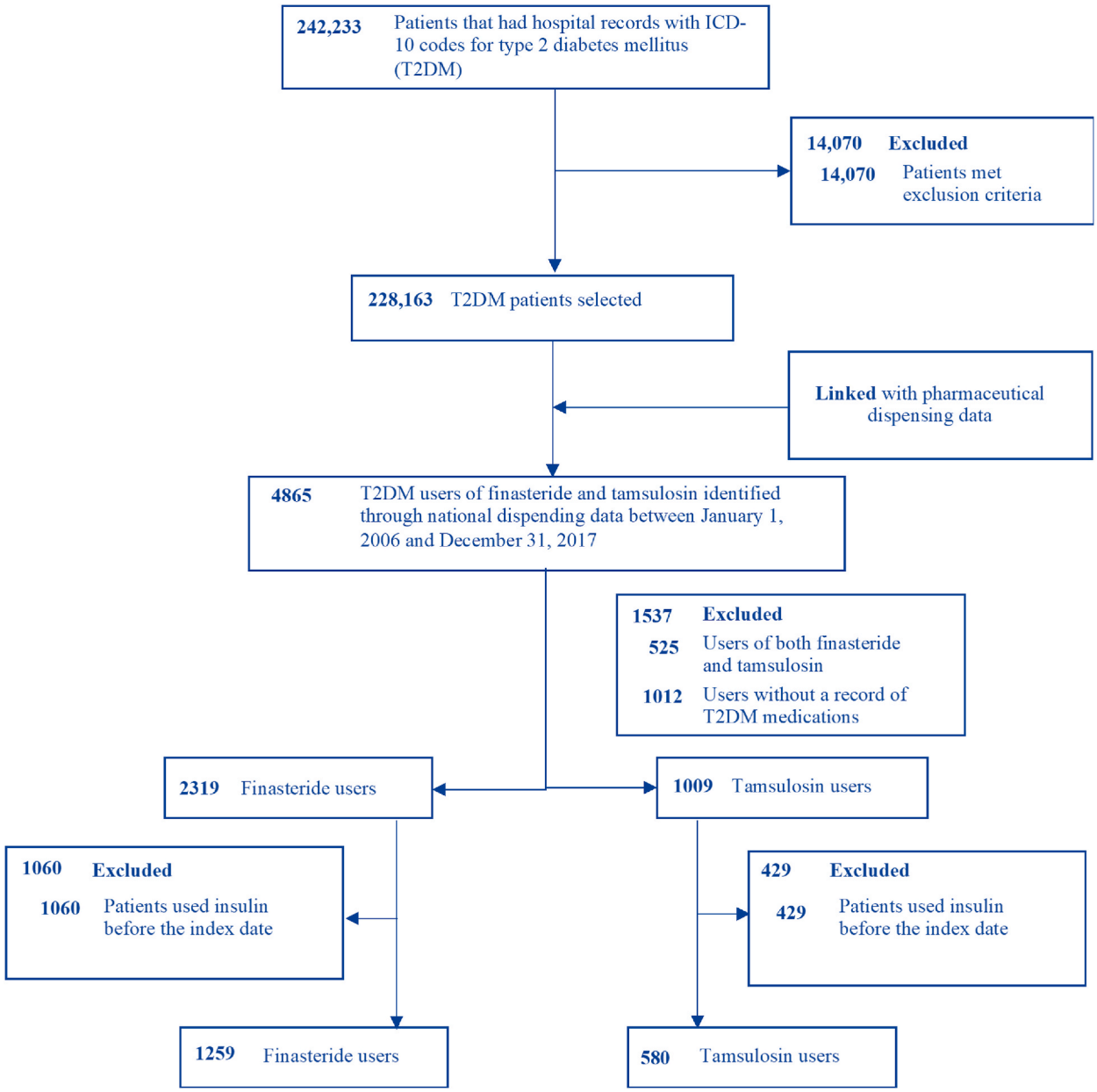


**Fig. 1.** Patient selection flow-chart.

Database, found finasteride—a 5-ARi—decreased the risk of developing T2DM [14]. By contrast, the latter study, which utilized both the National Health Insurance Research Database and the Clinical Practice Research Datalink database, showed finasteride increased the risk of T2DM [15]. Notably, neither study incorporated a lag period to address protopathic bias, which refers to reverse associations between drug exposure and the development of a disease or condition.

Furthermore, the impact of BPH medications on glycemic control in patients with T2DM remains unclear. To date, no real-world pharmaco-epidemiological study has compared the effects of finasteride and tamsulosin on glycemic control in patients with T2DM. This nationwide population-based cohort study aimed to compare the incidence of poor glycemic control between finasteride and tamsulosin users with T2DM.

## 2. Participants and methods

### 2.1. Data source

All data were sourced from the New Zealand Ministry of Health national collections between January 1, 2006 and 31 December 2017. Information on demographics (age, sex, and ethnicity), diagnosis date, and diagnosis code (based on the International Statistical Classification of Diseases, tenth edition [ICD-10]) was sourced from the National Minimum Dataset (hospital event data) [16]. The hospital event data were then linked with Pharmaceutical Dispensing data (containing claim and payment information from pharmacists) and mortality data using the encrypted National Health Index number—a unique identifier assigned to every person who utilizes health and disability services in New Zealand.

### 2.2. Study cohort

We used an active-comparator, new-user design to construct a cohort of men who were admitted for T2DM (ICD-10, E11) and then received either tamsulosin or finasteride treatment (Fig. 1). To increase the likelihood that selected patients indeed had T2DM, we further restricted our cohort to those who received at least 1 prescription for any oral diabetic medications during the study period following their admission with T2DM. Our search algorithm includeed all subsidized oral anti-diabetic medications in New Zealand during the study period, which were metformin, sulfonylureas, thiazolidinediones, and alpha-glucosidase inhibitors. To identify new users of the interest drugs, a 2-year wash-out period was applied, and patients required to have at least of 1-year of record pharmaceutical dispensing data to enter the study. For a head-to-head comparison between finasteride monotherapy and tamsulosin monotherapy, we identified the first date of the finasteride or tamsulosin prescription (set as index date) after December 31, 2007. We excluded 1) patients who had ICD-10 codes for other types of diabetes (E10, E12, E13, and E14), 2) patients who received an insulin prescription prior to the index date, 3) patients who switched from finasteride to tamsulosin or vice versa, 4) patients who received both tamsulosin and finasteride during the follow-up period, 5) patients with any cancer diagnosis during the study duration using relevant ICD-10 codes (C00–C97), and 6) patients who received fewer than three prescriptions for tamsulosin or finasteride.

### 2.3. Outcome and covariates

The outcome was the first insulin prescription, as a proxy for poor glycemic control [17] during the follow-up period. The follow-up period ended at the occurrence of the outcome, death, or December 31, 2017, whichever occurred first. The following potential confounders were considered: age at the index date, ethnicity, anti-diabetic medications, duration of T2DM (calculated from the first record of T2DM in the database to the index date), Charlson Comorbidity Index (CCI; based on ICD-10 codes in the 5 years prior to the index date), and the use of other drugs affecting glycemic control, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), diuretics, statins, and beta-blockers. In New Zealand, T2DM patients of some ethnicities have been reported to have poorer health outcomes than the majority ethnicity [18,19]. The ethnic groups were categorized as Europeans, Indigenous people, Asians, and others (including not stated cases) based on the codes provided by the New Zealand health ministry [20]. The baseline covariates were taken within one year prior to the index date unless otherwise stated.

### 2.4. Statistical analyses

#### 2.4.1. Main analysis

A log-rank test was conducted to investigate the significance of the difference in the probability of poor glycemic control (insulin-free probability) between finasteride and tamsulosin users during the follow-up period. A Kaplan-Meier curve was fitted on the unweighted population. We first estimated the crude hazard ratio between tamsulosin and finasteride, without any covariates. A 95 % confidence interval (CI) was used to account for uncertainty of the estimates and absolute difference less than 0.1 is deemed as suitable. Subsequently, we built a Cox proportional hazard model including the covariates (age at the index date, ethnicity, anti-diabetic medications, duration of T2DM, CCI, and use of ACEis, ARBs, diuretics, statins, and beta-blockers) and estimated adjusted hazard ratio (HR) and 95 % CI. The follow-up time for each patient was calculated as the time from the index date to the end of the follow-up period. The proportionality assumptions were not violated based on Schoenfeld proportionality tests. To address indication bias, we conducted inverse probability treatment weighting (IPTW). We first constructed a logistic regression model to obtain a propensity score for each patient using the above covariates; and then applied IPTW using the propensity scores to create a weighted population with balanced covariates. Extreme weights were removed with 1 % and 99 % quantile weight trimming. We evaluated baseline

covariates using the absolute standardized difference, cumulative distribution functions, and box plots (Figs. S1–3). Absolute standardized differences smaller than 0.10 were considered acceptable [21]. A Cox proportional hazard model was fitted after IPTW without including any covariates. Statistical analyses were carried out using Python 3.9.12 and RStudio (4.3.2).

#### 2.4.2. Sensitivity analysis

We conducted two sensitivity analyses to assess the robustness of our findings. First, to address protopathic bias and indication bias, we performed a delayed event analysis with 3-, 6-, 9-, and 12-month lag periods. These lag periods were chosen because 5-ARis may disrupt glucose metabolism between 3 weeks and 3 months from initiation [10,22]. Additionally, given the uncertainties regarding the time between worsening glycemic control and the first insulin prescription, we extended the exposure lag period to 12 months. This 12-month lag period was chosen because, on average, 1 year may elapse before providers intensify treatment for patients with poor glycemic control [23]. Patients experiencing the event of interest before the lag periods were likely influenced by protopathic bias. In the context of protopathic bias, tamsulosin is often prescribed to manage frequent micturition [24,25], which could indicate worsening of underlying diabetic symptoms. In this analysis, patients who received insulin during the lag periods were reclassified as non-events.

For the second sensitivity analysis, considering that patients with multiple comorbidities are more likely to receive insulin for glycemic control [26], the cohort was stratified as a low CCI stratum (i.e., patients with lower than or equal to the median CCI score of 9.0) and a high CCI stratum (i.e., patients with a CCI score higher than the median). Subsequently, IPTW using propensity score was applied as detailed above to create pseudo-populations, and a Cox proportional hazard model was fitted to estimate a weighted HR for each stratum. All sensitivity analyses were conducted using the pseudo-populations.

## 3. Results

### 3.1. Characteristics of the study cohort

We identified 1,259 finasteride users and 580 tamsulosin users among 228,163 patients with T2DM. At baseline, the tamsulosin group had a lower mean CCI score, and was more likely to use ARBs and statin while less likely to use ACEis, compared with the finasteride group (Table 1). After applying IPTW, all the absolute standardized differences in covariates were less than 0.10.

### 3.2. Risk of poor glycemic control in tamsulosin versus finasteride users

During a median follow-up of 2.44 years for finasteride users and 1.61 years for tamsulosin users, we noted 221 new insulin prescriptions (154 finasteride users and 67 tamsulosin users). The incidence rates were 564 per 10,000 person-years (95 % CI, 429–700) and 409 per 10,000 person-years (95 % CI, 344–474) in tamsulosin users and finasteride users, respectively (Table 2). The free-insulin prescription probability was lower in the tamsulosin cohort compared with the finasteride cohort ($p = 0.068$ from the log-rank test). The curve showed a rapid divergence after treatment initiation (Fig. 2). Tamsulosin users had a higher insulin prescription rate compared with finasteride users, although this increased risk was not statistically significant (adjusted HR, 1.23; 95 % CI, 0.92–1.66). After IPTW, a similar risk of receiving an insulin prescription was observed in tamsulosin users versus finasteride users

**Table 1**
Baseline characteristics of tamsulosin and finasteride users before and after applying inverse probability weighting.

| Characteristics | Before weighting | | | After weighting[a] | | |
|---|---|---|---|---|---|---|
| | Tamsulosin (n = 580) | Finasteride (n = 1259) | ASD[b] | Tamsulosin (n = 1836) | Finasteride (n = 1837) | ASD[b] |
| Age, years, mean (SD) | 74.77 (8.69) | 75.24 (8.29) | 0.055 | 75.08 (8.63) | 75.10 (8.30) | 0.00 |
| Comorbidity index, mean (SD) | 9.50 (5.46) | 10.05 (5.75) | 0.099 | 9.87 (5.66) | 9.89 (5.66) | 0.00 |
| Diabetes duration, mean (SD) | 6.08 (4.89) | 5.78 (4.51) | 0.063 | 5.83 (4.83) | 5.87 (4.53) | 0.01 |
| Anti-diabetic drug, No. (%) | | | | | | |
| Metformin | 472 (81.38) | 1003 (79.67) | 0.043 | 1476 (80.40) | 1473 (80.20) | 0.01 |
| Sulfonylureas | 274 (47.24) | 567 (45.04) | 0.044 | 837 (45.58) | 838 (45.63) | 0.00 |
| Other drug use, No. (%) | | | | | | |
| ACE[b] inhibitors | 360 (62.07) | 852 (67.67) | 0.118 | 1213 (66.07) | 1213 (66.03) | 0.00 |
| ARBs[b] | 109 (18.79) | 186 (14.77) | 0.108 | 296 (16.13) | 294 (16.00) | 0.00 |
| Beta blocker | 310 (53.45) | 634 (50.36) | 0.062 | 947 (51.58) | 943 (51.32) | 0.01 |
| Diuretics | 243 (41.90) | 476 (37.81) | 0.084 | 709 (38.62) | 715 (38.90) | 0.01 |
| Statin | 496 (85.52) | 1028 (81.65) | 0.104 | 1524 (83.03) | 1521 (82.79) | 0.01 |
| Ethnicity, No. (%) | | | 0.04 | | | 0.04 |
| European | 406 (70.00) | 903 (71.72) | | 1313 (71.51) | 1309 (71.26) | |
| Asian | 61 (10.52) | 144 (11.44) | | 202 (11.01) | 205 (11.16) | |
| Indigenous | 82 (14.14) | 138 (10.96) | | 219 (11.95) | 218 (11.84) | |
| Not stated/others | 31 (5.34) | 74 (5.88) | | 102 (5.54) | 105 (5.70) | |

[a] Pseudo population created by applying inverse probability treatment weighted from propensity score.
[b] ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, ASD = absolute standardized difference, SD = standard deviation.

**Table 2**
Risks of insulin prescriptions associated with tamsulosin monotherapy versus finasteride monotherapy in patients with type 2 diabetes mellitus.

| Exposure | Patients | Events | Incidence rate[a] (95 % CI) | Crude HR (95 % CI) | Adjusted HR (95 % CI) | Weighted HR[b] (95 % CI) |
|---|---|---|---|---|---|---|
| Tamsulosin | 580 | 67 | 564 (429–700) | 1.31 (0.98–1.75) | 1.23 (0.92–1.66) | 1.27 (0.95–1.72) |
| Finasteride | 1259 | 154 | 409 (344–474) | | | |

HR = hazard ratio, CI = confidence interval.
Finasteride is the reference group.
[a] Per 10,000 person-years.
[b] The models were weighted using inverse probability weighting.

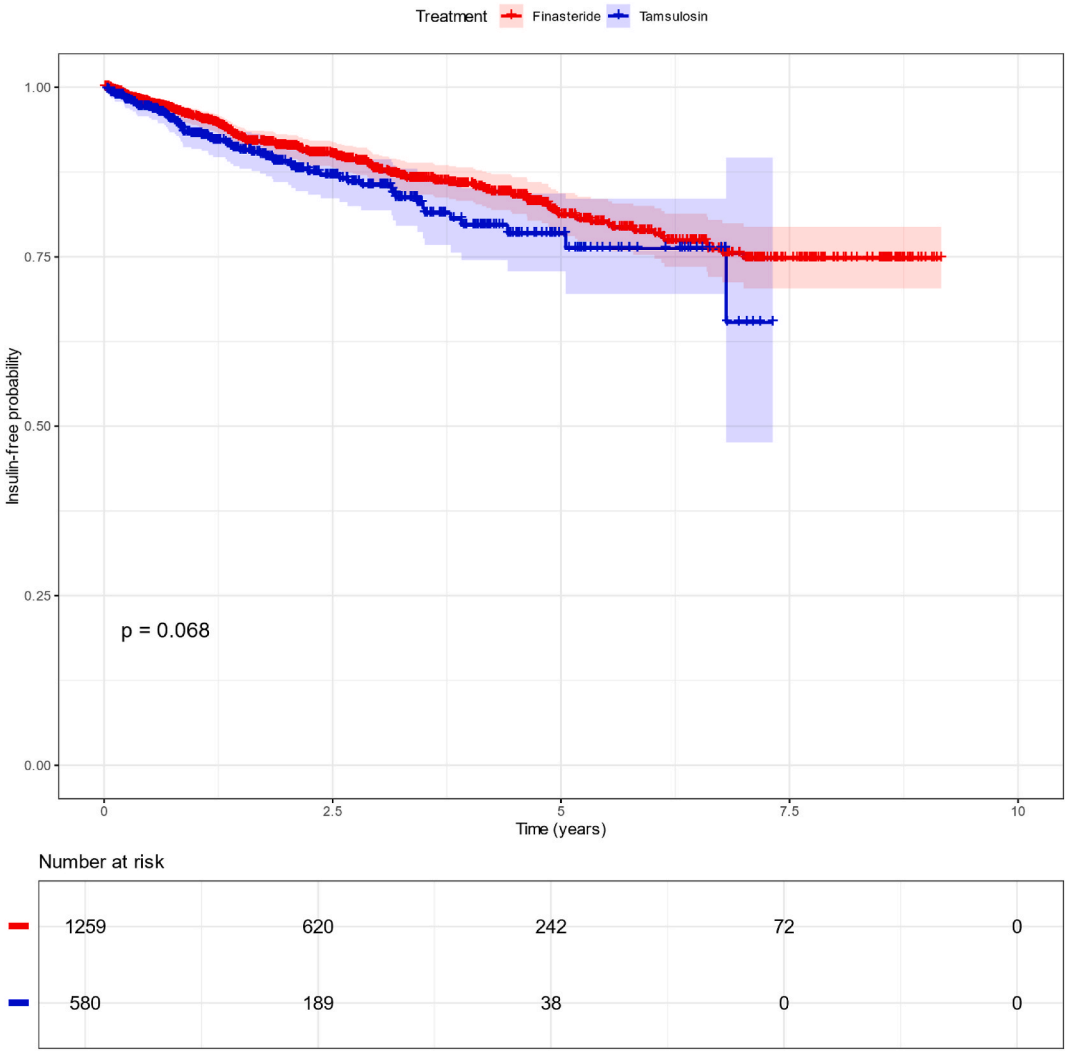


**Fig. 2.** Insulin-free probability of the finasteride monotherapy and tamsulosin monotherapy groups (unweighted).

(weighted HR, 1.27; 95 % CI, 0.95–1.72).

### *3.3. Sensitivity analyses*

With each successive application of lag periods, the risk of receiving an insulin prescription associated with tamsulosin monotherapy versus finasteride monotherapy gradually decreased. In weighted populations, the risks of receiving an insulin prescription were 24 %, 26 %, 23 %, and 15 % higher in tamsulosin users compared with finasteride users when applying 3-, 6-, 9-, and 12-month lag periods, respectively (Table S1). The risks were not statistically significant. In the CCI-stratified analyses, the insulin prescription risks associated with tamsulosin monotherapy versus finasteride monotherapy increased by 34 % and 20 % for the lower stratum and

higher stratum, respectively (Fig. 3; Table S2).

## 4. Discussion

This nationwide population-based cohort study estimated the risk of insulin prescription (as a proxy for poor glycemic control) in tamsulosin users compared with finasteride users among individuals with T2DM. While there are controversies surrounding the relationship between 5-ARis and the heightened risk of T2DM, our study adds to current evidence on the effect of BPH medication on glycemic control in patients with T2DM. In our main analysis, tamsulosin users were at a higher risk of poor glycemic control compared with finasteride users (HR = 1.23), but this risk did not reach statistical significance. Additional analyses addressing indication bias (IPTW using propensity scores) and protopathic bias (applying lag periods at 3-month intervals, ranging from 3 to 12 months) demonstrated similar risks.

The effect of BPH medications on glycemic control may be dynamic with various pathways. Although earlier studies have not unequivocally established the causality between 5-ARis and worsening glycemic control (leading to the development of T2DM), a considerable body of evidence indicates that use of 5-ARis may reduce insulin sensitivity in non-diabetic individuals via steatotic liver disease [8–10,15]. The persistent trend of elevation of insulin prescription risk in the tamsulosin group in the present study suggests that tamsulosin might contribute to the worsening of glycemic control in patients with T2DM. Studies on non-insulin-dependent glucose metabolism pathways in human adipose tissue [27,28] have shown that the inhibition of alpha receptors (by alpha receptor blockers) decreases glucose uptake, thereby worsening glycemic control. In the present study, the hazard rate of poor glycemic control was higher in tamsulosin users compared with finasteride users among individuals with T2DM. The possibility that tamsulosin exacerbates glycemic control in T2DM patients with excess adipose tissue appeared in a few case reports. Four T2DM patients with well-controlled blood glucose developed hyperglycemia within 48 h of initiating tamsulosin; the patients' blood glucose levels more than doubled after tamsulosin initiation and decreased to normal levels after discontinuing tamsulosin, and all other potential causes of hyperglycemia were ruled out [13].

The present study may have clinical implications for the use of BPH medications in patients with T2DM. Previous real-world evidence from the UK and Canada suggests that 5-ARi users may have a risk of developing T2DM compared with tamsulosin users in BPH patients with normoglycemia [15,29]. It is noteworthy that the latter study did not find a dose-response relationship in 5-ARi users [29]. In our study, the results demonstrated no significant difference in the risk of poor glycemic control between finasteride users and tamsulosin users, with increasing follow-up time among patients with T2DM. This suggests that 5-ARis and tamsulosin may not differentially affect glycemia after T2DM has developed. We attempted to address the indication bias due to the different patient characteristics related to finasteride and tamsulosin prescriptions using IPTW with propensity scores, which yielded similar risks. One could also argue that protopathic bias or reverse causation may affect the risk of receiving an insulin prescription in the tamsulosin

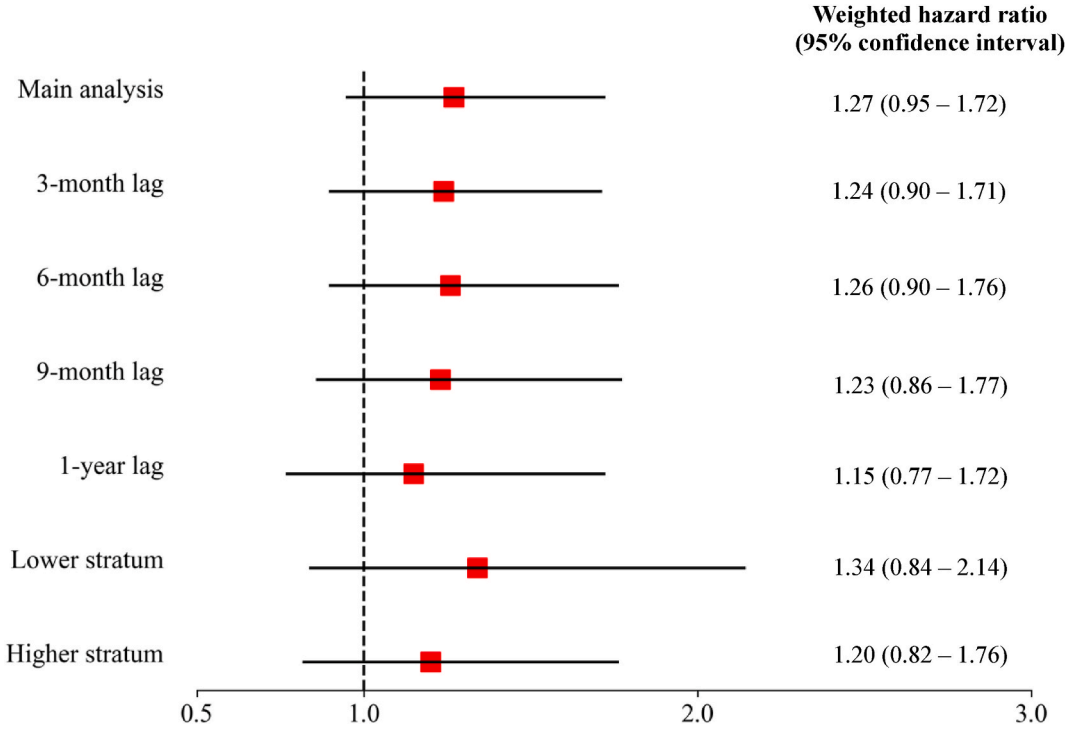


**Fig. 3.** Forest plot summarizing weighted hazard ratios and 95 % CIs of risk of insulin prescriptions associated with tamsulosin monotherapy versus finasteride monotherapy (lower stratum: Charlson comorbidity index (CCI) ≤ 9 [median], higher stratum: CCI >9).

group versus the finasteride group. However, our additional analyses using 3- to 12-month lag periods, with 3-month intervals, displayed similar risk estimates. Furthermore, the effect of protopathic bias may be minimal because poor glycemic status exacerbates BPH [30,31] and patients with severe BPH are more likely to receive finasteride over tamsulosin. Hence, our findings suggest that, over the long term, finasteride users may not experience more hyperglycemia episodes than if they had been prescribed tamsulosin. However, there might be an elevation of risk during the initial phase of tamsulosin in new users with T2DM.

This study has several limitations that should be acknowledged. First, prescription of insulin was used as a surrogate endpoint for poor glycemic control. This approach may have underestimated the number of individuals with poor glycemic control because it did not account for changes from metformin monotherapy to combination therapy with other oral anti-diabetic medications in defining poor glycemic control. During the study period from 2006 to 2017, relatively new oral anti-diabetic medications (e.g., dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitors, and glucagon-like peptide-1 receptor agonists) were not yetintroduced or publicly funded in New Zealand. Insulin has been recommended as an initial treatment for severe hyperglycemia and a third-line treatment for uncontrolled T2DM after combination therapy [35]. Since these indications of insulin prescriptions are based on the level of hemoglobin A1c, insulin use may serve as a useful proxy for poor glycemic control in studies using pharmaceutical dispensing data. Second, we used hospital discharge data to identify individuals with T2DM. This means that we captured more severe cases of T2DM, possibly with comorbidities. To address the potential effect of comorbidity on the studied associations, we estimated the risk of receiving an insulin prescription associated with tamsulosin use versus finasteride use after stratification by CCI score. The risk remained elevated in both the low and high strata of CCI score. Third, there may have been unmeasured confounders. For example, we did not include other possible hyperglycemia-inducing drugs (such as corticosteroids, second-generation antipsychotics, protease inhibitors and calcineurin inhibitors) in the study because our patients did not have a record (protease inhibitors and calcineurin inhibitors) or a very small number of patients were on them (second-generation antipsychotic and corticosteroids). Another example is socioeconomic status, as low socioeconomic status is associated with more severe symptoms of BPH [32] as well as poor glycemic control [33,34]. Although we included ethnicity as a covariate to control for socioeconomic status, the social deprivation index may be useful as another covariate to include in the model. Lastly, the prescription data only included drugs publicly funded in New Zealand. Our study cohort spanned from 2008 to the end of 2017. Although tamsulosin was not publicly funded until August 2010, we applied the same time period to the finasteride and tamsulosin cohorts (from January 2008). This is unlikely to have distorted our results, as we employed a dynamic cohort design.

In conclusion, the present study demonstrated that finasteride users and tamsulosin users had similar risks of poor glycemic control with long-term use of these drugs among individuals with T2DM. However, there may be an increased risk during the initiation of tamsulosin in BPH-treatment-naïve patients with T2DM. Further studies with longer follow-up periods and larger sample sizes are required to confirm these associations.

## Ethics and consent

Ethics approval was waived because we obtained de-identified raw data from New Zealand Ministry of Health national collections for research purpose (https://www.tewhatuora.govt.nz/for-health-professionals/data-and-statistics/nz-health-statistics/national-collections-and-surveys/collections/national-minimum-dataset-hospital-events). This study used secondary data and thus did not require informed consent from individual patients. There were no data of people under 18 years old in this study.

## CRediT authorship contribution statement

**Minh-Ha Nguyen:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Maxim S. Petrov:** Writing – review & editing, Methodology, Data curation. **Jaelim Cho:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

## Data and code availability statement

The authors do not have permission to share data. The code used for this study is publicly available at: https://github.com/minhha0510/NewZealand–5ARi-uses-and-diabetes-risk.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Minh-Ha Nguyen reports that financial support was provided by Korea International Cooperation Agency. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e41768.

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