Clinical science

Risk of glaucoma among patients using tadalafil for lower urinary tract symptoms: a multinational cohort study

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ABSTRACT

Aim To evaluate the association between tadalafil use for lower urinary tract symptoms (LUTS) and the risk of developing glaucoma.

Methods This multinational, retrospective cohort study was conducted using the TriNetX database. Men aged ≥40 years with a history of LUTS were enrolled between 2012 and 2022. Individuals with a history of glaucoma prior to cohort entry were excluded. Participants were categorised into the tadalafil group and the non-phosphodiesterase type 5 inhibitor (non-PDE5i) group. Propensity score matching (1:1) was conducted to balance age, race, comorbidities, renal function and concomitant medications. Hazard ratios (HRs) were estimated for incident glaucoma of different subtypes and initiation of glaucoma treatment.

Results The cohort included 36 927 tadalafil users and 36 927 matched non-PDE5i users. Up to 5 years, tadalafil use was associated with an increased risk of glaucoma compared with non-PDE5i use (HR 1.22; 95% CI 1.12 to 1.33). Elevated risks were observed for ocular hypertension (HR 1.32; 95% CI 1.06 to 1.65), primary open-angle glaucoma (HR 1.33; 95% CI 1.05 to 1.67) and initiation of glaucoma treatment (HR 1.33; 95% CI 1.20 to 1.47). No significant associations were found for low-tension or primary angle-closure glaucoma. Tadalafil users had a higher 5-year cumulative incidence than non-users (3.93% vs 3.16%; p<0.001), with consistent risk in men >50 years, white population and across comorbidities, remaining robust to 1-, 3- and 6-month lag times.

Conclusions Tadalafil was associated with increased risk of glaucoma compared with non-PDE5i in males with LUTS. Ophthalmic evaluation and follow-up may be considered, particularly in patients with risk factors for glaucoma.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Phosphodiesterase type 5 inhibitors (PDE5i), such as sildenafil used for erectile dysfunction, have been associated with various ocular adverse events including optic neuropathy and maculopathy. Evidence regarding the potential association between PDE5i and glaucoma remains limited and inconclusive, particularly for tadalafil prescribed for lower urinary tract symptoms (LUTS), which typically involves long-term daily dosing.

WHAT THIS STUDY ADDS

⇒ Tadalafil use for LUTS was associated with a significant increase in the risk of glaucoma, ocular hypertension, primary open-angle glaucoma and initiation of glaucoma treatment in a large, multinational, real-world cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that chronic PDE5 inhibition may influence ocular physiology, warranting further mechanistic investigation. Clinically, enhanced ophthalmic monitoring may be considered for patients receiving long-term tadalafil, particularly those with glaucoma risk factors.

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INTRODUCTION

Phosphodiesterase type 5 inhibitors (PDE5i) are widely prescribed for the treatment of pulmonary arterial hypertension, erectile dysfunction and lower urinary tract symptoms (LUTS).[1] These agents exert their therapeutic effects by inhibiting the PDE5 enzyme, leading to increased intracellular levels of cyclic guanosine monophosphate (cGMP). The accumulation of cGMP promotes smooth muscle relaxation and vasodilation within target tissues,[2] and has been associated with several systemic adverse effects including headache, flushing,[3] sensorineural hearing loss[4] and orthostatic hypotension.[5]

Although several ocular adverse effects of PDE5i have been reported, including rare but serious events such as serous retinal detachment, retinal vascular occlusion and ischaemic optic neuropathy, the association between PDE5i use and glaucoma remains controversial.[6 7] The likelihood of these complications appears to correlate with treatment intensity.[8] However, the mechanistic evidence is conflicting.[9 10] PDE5i-induced vasodilation may theoretically cause transient intraocular pressure (IOP) elevation through increased fluid passage from ciliary body capillaries,[11] yet clinical studies

have not consistently demonstrated sustained IOP elevation with chronic use.[12] Similarly, while systemic hypotension may lead to optic nerve hypoperfusion, potentially contributing to non-arteritic anterior ischaemic optic neuropathy (NAION)[6] or normal-tension glaucoma,[9] other studies suggest that PDE5i may enhance choroidal and retrobulbar blood flow, effects that could be protective or neutral in the long-term course of glaucoma.[13–15] Given these conflicting physiological effects, large population-based studies are needed to clarify the relationship between PDE5i use and glaucoma risk.

Tadalafil, a long-acting PDE5i, is approved for the management of LUTS associated with benign prostatic hyperplasia (BPH). Unlike the intermittent dosing regimen commonly used for erectile dysfunction, patients with LUTS typically receive tadalafil on a continuous, daily basis. This prolonged exposure may potentially amplify the medication's cumulative effects on IOP regulation and ocular blood flow. Therefore, we aimed to investigate the association between long-term tadalafil use for LUTS and the risk of developing glaucoma.

METHODS

Data source

This study utilised de-identified patient-level data extracted from the TriNetX Analytics Network (Global Collaborative Network) and was conducted in October 2025. TriNetX is a federated, cloud-based research platform that enables large-scale analyses of real-world clinical data and integrates anonymised electronic health records contributed by more than 160 healthcare organisations, representing over 200 million patients across 21 countries. The network provides access to comprehensive longitudinal information, including demographic characteristics, diagnoses, medications, laboratory results and procedures. To safeguard privacy, all data are de-identified in compliance with applicable regulations. The platform also enforces an additional privacy rule that prohibits analyses involving cohorts of fewer than 10 patients.

Study design

This retrospective cohort study included male patients with LUTS who initiated treatment with tadalafil, a PDE5i, and a comparison cohort of individuals who did not receive any PDE5i, including tadalafil, sildenafil, avanafil and vardenafil, between January 2012 and December 2022. Enrolment concluded in December 2022 to allow adequate follow-up time. The date of the first tadalafil prescription was designated as the index date, and each participant was observed for up to 5 years. Follow-up was terminated at the earliest occurrence of the outcome event or the end of the study period. The primary outcome was the incidence of glaucoma (H40) recorded in outpatient or inpatient encounters after the index date. We also investigated the risk of ocular hypertension (H40.05), primary open-angle glaucoma (H40.11), normal-tension glaucoma (H40.12), primary angle-closure glaucoma (H40.2) and the commencement of glaucoma treatment. The risk was compared between the tadalafil and non–PDE5i cohorts at 5-year follow-up intervals.

Study population

Our inclusion criteria for the tadalafil group were as follows: (i) male patients aged ≥40 years and (ii) initiation of tadalafil for the treatment of LUTS between January 2012 and December 2022. We also limited inclusion to individuals who had either a refill or an ongoing prescription for the medication between 3 and 12 months after the initial prescription. Patients who had a diagnosis of any subtype of glaucoma before the index date were excluded. The non-PDE5i group comprised male individuals

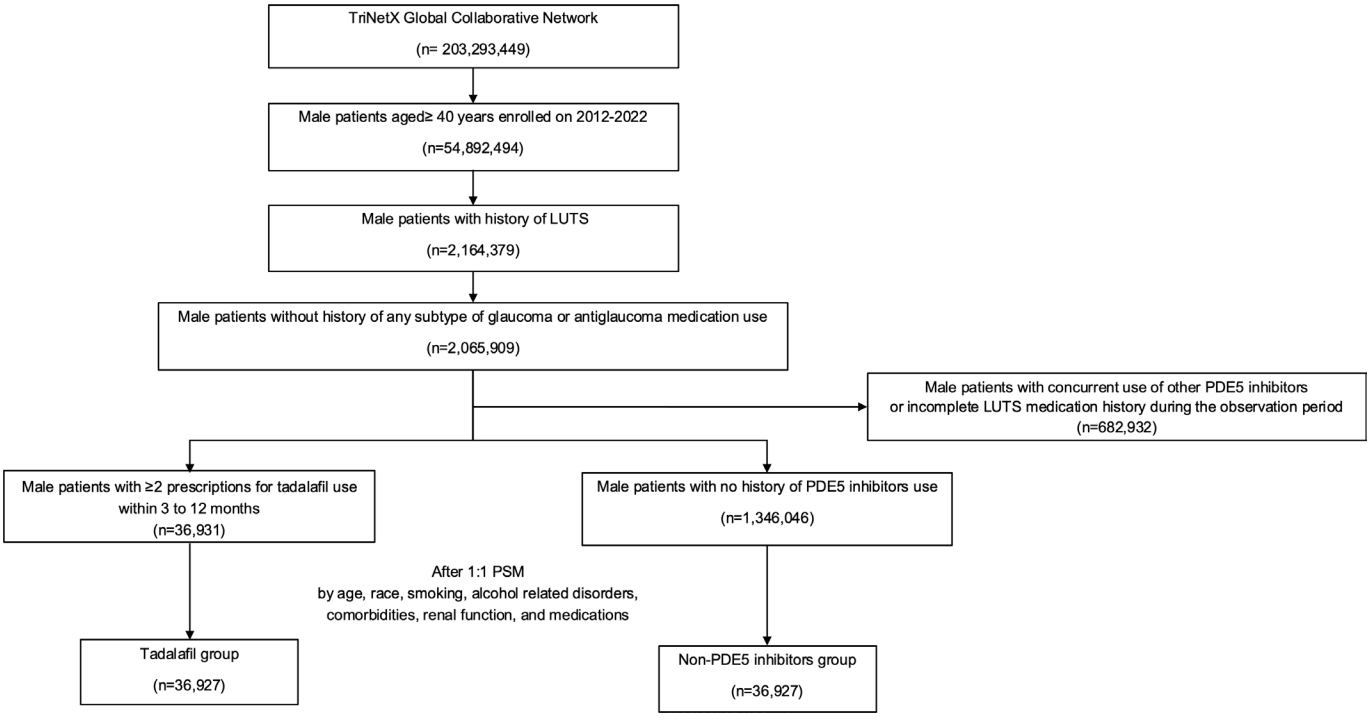

Figure 1 Study flowchart showing the construction of the multinational cohort used to examine the association between tadalafil use for lower urinary tract symptoms (LUTS) and glaucoma risk. After exclusion of individuals with pre-existing glaucoma and other predefined criteria, eligible patients were classified according to tadalafil exposure. Propensity score matching (PSM) was performed to generate comparable tadalafil user and non-phosphodiesterase type 5 (non-PDE5) inhibitors user cohorts for longitudinal follow-up.

with a documented history of LUTS who had no prior exposure to PDE5i. Participants with a pre-existing diagnosis of glaucoma or incomplete LUTS treatment records were excluded.

We performed 1:1 propensity score matching using age, race (white, black or African American and Asian), smoking, alcohol-related disorders, comorbidities (hypertension, type 2 diabetes mellitus, neoplasms, ischaemic heart disease, cerebrovascular diseases, heart failure, atrial fibrillation, dyslipidaemia, obesity and chronic obstructive pulmonary disease), glomerular filtration rate and medications (corticosteroids, alpha-blockers, testosterone-5-alpha reductase inhibitors and anticholinergic agents) as covariates.[16 17] To ensure accurate matching, we only incorporated covariates within 1 year before the index date. A greedy nearest-neighbour algorithm with a calliper of 0.1 pooled SD was adopted. The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) and other codes used to determine each prescription or diagnosis are provided in online supplemental table 1.

The follow-up periods were 5 years. Given the established associations between glaucoma and demographic as well as systemic risk factors, prespecified subgroup analyses were conducted to explore potential effect modification. Stratification was performed by age (<50 vs ≥50 years), race (White, Black and Asian) and key comorbidities (hypertension, type 2 diabetes mellitus, hyperlipidaemia, obesity and chronic kidney disease) to examine the consistency and stability of the estimated hazard ratios (HRs) across clinically relevant strata. HRs and 95% CIs were estimated using Cox proportional hazards regression models. Kaplan–Meier methods were applied to estimate cumulative incidence and to illustrate survival probabilities over the follow-up period. The study protocol for this retrospective analysis using data from the TriNetX platform was reviewed and approved by the Institutional Review Board of Taichung Veterans General Hospital.

RESULTS

The final analysis included 36 927 males with LUTS in the tadalafil group, and 36 927 males with LUTS were matched as non-PDE5i users. The mean age was 62.1±9.4 and 62.3±9.6 years in the tadalafil and non-PDE5i groups, respectively. The study flowchart is shown in figure 1. After following individuals for up to 5 years, the development of incident glaucoma and requirement for glaucoma medications and/or laser treatment were observed. Baseline characteristics are well-balanced between participants prescribed with tadalafil and non-PDE5i users with all standardised mean differences<0.1 (table 1).

Glaucoma risk at 5 years

Over 5 years of follow-up, compared with non-PDE5i users, those on tadalafil are associated with a significantly greater risk of glaucoma (HR 1.22; 95% CI 1.12 to 1.33), ocular hypertension (HR 1.32; 95% CI 1.06 to 1.66), primary open-angle glaucoma (HR 1.33; 95% CI 1.05 to 1.67) and receiving first-line

Table 1 Baseline characteristics of the study cohorts

	Before matching			After matching		
Characteristic	Tadalafil	Non-PDE5i	SMD	Tadalafil	Non-PDE5i	SMD
Total number, n	36 931	1 346 046		36 927	36 927	
Age (years), mean±SD	62.1±9.4	63.3±11.1	0.114	62.1±9.4	62.3±9.6	0.019
Race, n (%)						
White	26 354 (71.4)	918 113 (68.2)	0.069	26 354 (71.4)	26 724 (72.4)	0.022
Black	4831 (13.1)	116 795 (8.7)	0.142	4827 (13.1)	4510 (12.2)	0.026
Asian	830 (2.2)	63 082 (4.7)	0.134	830 (2.2)	827 (2.2)	0.001
Smoking, n (%)	554 (1.5)	20 749 (1.5)	0.003	554 (1.5)	462 (1.3)	0.021
Alcohol-related disorders, n (%)	684 (1.9)	25 323 (1.9)	0.002	684 (1.9)	607 (1.6)	0.016
Comorbidities, n (%)						
Hypertension	15 597 (42.2)	435 004 (32.3)	0.206	15 593 (42.2)	15 653 (42.4)	0.003
Type 2 diabetes mellitus	5943 (16.1)	194 379 (14.4)	0.046	5941 (16.1)	5980 (16.2)	0.003
Hyperlipidaemia	14 989 (40.6)	361 993 (26.9)	0.293	14 985 (40.6)	14 972 (40.5)	0.001
Neoplasms	9754 (26.4)	203 533 (15.1)	0.281	9750 (26.4)	9713 (26.3)	0.002
Ischaemic heart disease	4012 (10.9)	151 726 (11.3)	0.013	4012 (10.9)	3842 (10.4)	0.015
Cerebrovascular disease	1144 (3.1)	56 978 (4.2)	0.060	1144 (3.1)	1040 (2.8)	0.017
Heart failure	962 (2.6)	52 567 (3.9)	0.073	962 (2.6)	837 (2.3)	0.022
Atrial fibrillation	1850 (5.0)	74 735 (5.6)	0.024	1850 (5.0)	1715 (4.6)	0.017
Obesity	4270 (11.6)	93 501 (6.9)	0.160	4267 (11.6)	4061 (11.0)	0.018
COPD	1253 (3.4)	58 358 (4.3)	0.049	1253 (3.4)	1084 (2.9)	0.026
Laboratory data, n (%)						
eGFR, mL/min/1.73 m^2						
<60	3593 (9.7)	138 138 (10.3)	0.018	3593 (9.7)	3467 (9.4)	0.012
≥60	18 523 (50.2)	458 875 (34.1)	0.330	18 519 (50.2)	18 618 (50.4)	0.005
Medications, n (%)						
Corticosteroids	10 919 (29.6)	240 657 (17.9)	0.277	10 915 (29.6)	10 905 (29.5)	0.001
Alpha-blockers	11 792 (31.9)	160 460 (11.9)	0.498	11 788 (31.9)	11 764 (31.9)	0.001
Reductase inhibitors	3336 (9.0)	39 155 (2.9)	0.261	3332 (9.0)	3230 (8.7)	0.010
Anticholinergic agents	282 (0.8)	6673 (0.5)	0.034	282 (0.8)	231 (0.6)	0.017

COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; PDE5i, phosphodiesterase type 5 inhibitor; SMD, standardised mean difference.

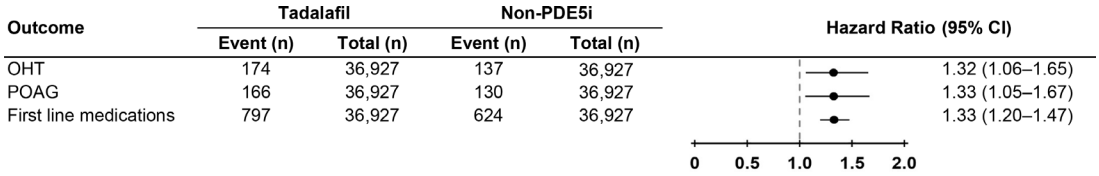

Figure 2 Glaucoma subtype-specific risk associated with tadalafil use. Forest plot illustratring the comparative risk of glaucoma-related outcomes between tadalafil users and non-phosphodiesterase type 5 inhibitors (non-PDE5i) users. OHT, ocular hypertension; POAG, primary open-angle glaucoma.

glaucoma treatment (HR 1.33; 95% CI 1.20 to 1.47) (figure 2). First-line glaucoma treatment was defined as using beta-blockers, prostaglandin analogues, brimonidine, dorzolamide, brinzolamide, netarsudil or laser therapies.[18] The risk of normal-tension glaucoma (HR 0.78; 95% CI 0.43 to 1.42) and primary angle-closure glaucoma (HR 0.89; 95% CI 0.50 to 1.57) were not significantly different between groups.

The 5-year Kaplan–Meier survival analysis indicated that patients prescribed tadalafil, compared with non-PDE5i users, had a greater cumulative probability of glaucoma (tadalafil user: 3.93%, non-PDE5i users: 3.16%; log-rank test, p<0.001) (figure 3), ocular hypertension (tadalafil user: 0.61%, non-PDE5i users: 0.47%; log-rank test, p=0.014), primary open-angle glaucoma (tadalafil user: 0.59%, non-PDE5i users: 0.43%; log-rank test, p=0.016) and glaucoma treatment (tadalafil user: 2.76%, non-PDE5i users: 2.05%; log-rank test, p<0.001) (online supplemental figure S1). However, the cumulative probability of normal-tension glaucoma (tadalafil user: 0.06%, non-PDE5i users: 0.08%; log-rank test, p=0.424) and primary angle-closure glaucoma (tadalafil user: 0.08%, non-PDE5i users: 0.09%; log-rank test, p=0.679) were not significantly different between tadalafil users and non-PDE5i users.

Glaucoma risk by different stratifications

Study participants are further categorised into different groups based on age, race and comorbidities. The risk of glaucoma was not significantly greater in the age group 40–50 years (HR 1.41; 95% CI 0.93 to 2.14), while tadalafil users older than 50 years had greater risk of glaucoma (HR 1.29; 95% CI 1.18 to 1.41). Among different races, tadalafil users had greater risk of glaucoma in the white group (HR 1.16; 95% CI 1.04 to 1.29). In the Asian group (HR 1.62; 95% CI 0.96 to 2.74), the HR did not reach statistical significance. When stratified by comorbidities, including hyperlipidaemia, obesity and chronic kidney disease, tadalafil users consistently had greater glaucoma risk than non-PDE5i users (figure 4).

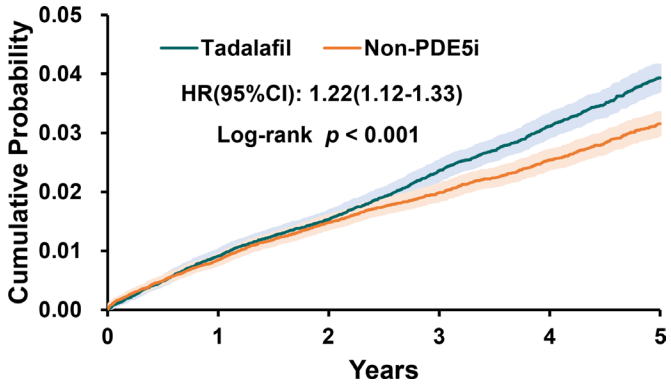

Figure 3 Cumulative probability of glaucoma according to tadalafil use. Kaplan–Meier curves showing the cumulative probability of glaucoma among tadalafil users and non-phosphodiesterase type 5 inhibitors (non-PDE5i) users. Differences between groups were assessed using the log-rank test.

Sensitivity analysis

We excluded patients with a diagnosis of glaucoma within the first 1, 3 or 6 months after starting tadalafil. The risk of glaucoma remained increased across all lag-time windows with HRs of 1.233 (95% CI 1.131 to 1.345), 1.232 (95% CI 1.129 to 1.344) and 1.230 (95% CI 1.126 to 1.344) for 1-, 3- and 6-month exclusions, respectively (online supplemental figure S2). To address potential detection bias arising from differential access to eye care, we performed an additional analysis incorporating prior ophthalmology visits as a matching covariate in the propensity score model. The results remained consistent with the primary analysis, with a persistently increased risk of glaucoma (HR 1.11; 95% CI 1.02 to 1.22) and glaucoma treatment initiation (HR 1.28, 95% CI 1.14 to 1.45).

DISCUSSION

In this large, population-based cohort study, tadalafil use for the management of LUTS was associated with an increased risk of glaucoma compared with non-PDE5i users. Similar trends were observed for the incidence of ocular hypertension and primary open-angle glaucoma, as well as for the need for glaucoma treatment. These associations remained robust after excluding individuals who developed glaucoma within 1, 3 or 6 months after tadalafil initiation, and were consistently observed among patients aged ≥50 years, white individuals and across subgroups with or without comorbidities, including hypertension, diabetes mellitus, hyperlipidaemia, obesity and chronic kidney disease. A previous review has recommended baseline ophthalmic screening before initiating regular PDE5i therapy, as well as periodic follow-up for individuals with glaucoma or predisposing risk factors.[19] This recommendation aligns with our findings, which also suggest the need for ocular monitoring in patients receiving long-term tadalafil treatment.

PDE5i act by enhancing the nitric oxide (NO)–cGMP signalling pathway. NO stimulates the conversion of guanosine triphosphate (GTP) to cGMP, and the subsequent elevation of intracellular cGMP reduces calcium concentrations, leading to smooth muscle relaxation and vasodilation. PDE5 is the enzyme responsible for degrading cGMP into inactive GMP; by selectively inhibiting PDE5, these drugs prevent cGMP breakdown, thereby prolonging and amplifying vasodilation in tissues where PDE5 is expressed. Therapeutic targets include the penile corpus cavernosum, pulmonary vasculature, lower urinary tract and prostate. PDE5 is also expressed in various ocular structures, including the retinal and choroidal vasculature, retinal pigment epithelium, retinal ganglion cells, photoreceptors, ciliary body, iris and optic nerve head.[20] Previous studies have reported diverse ocular effects of PDE5i. Administration of sildenafil

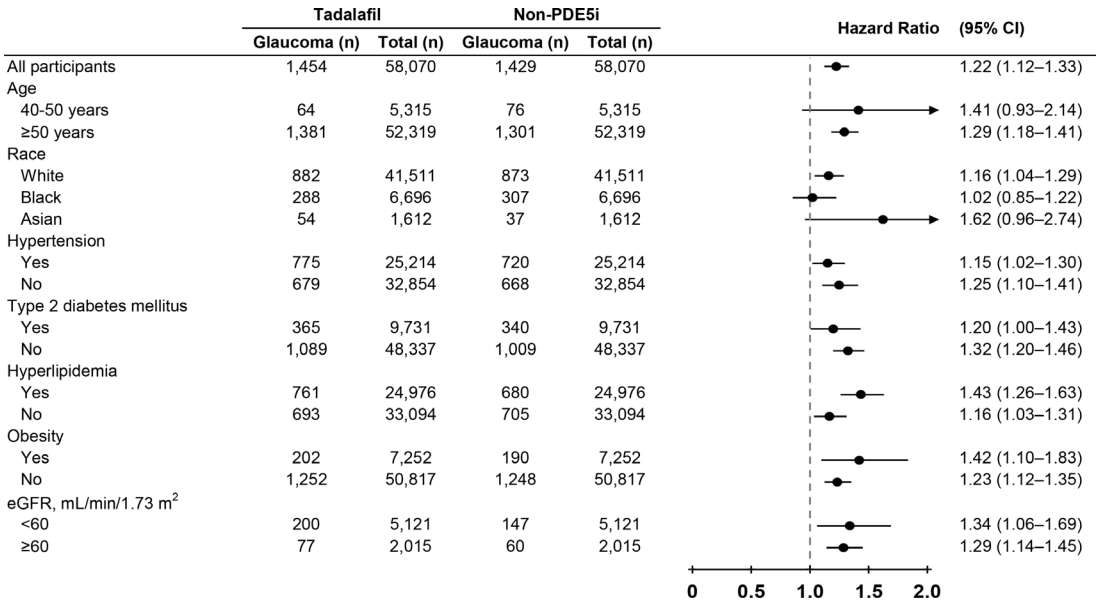

Figure 4 Subgroup analysis of glaucoma risk associated with tadalafil use. Forest plot illustrating the subgroup analysis of comparative risk of glaucoma between tadalafil users and non-phosphodiesterase type 5 inhibitors (non-PDE5i) users. eGFR, estimated glomerular filtration rate.

has been shown to cause transient IOP elevation and increased protein concentration in the aqueous humour.[21] The proposed mechanism involves vasodilation of the ciliary body vasculature, which may enhance aqueous humour production and transiently raise IOP. Although the effect is temporary, repeated short-term IOP elevation could contribute to insidious glaucomatous damage over time. Conversely, activation of the NO–cGMP pathway has also been shown to relax trabecular meshwork cells, potentially facilitating aqueous humour outflow and lowering IOP.[22] The net impact of these opposing mechanisms on IOP and glaucoma risk remains uncertain. Clinical studies examining the effects of PDE5i on IOP are limited by small sample sizes, lack of control groups or the predominance of healthy participant enrolment, yielding inconsistent results.[19 23] One prior population-based study investigating sildenafil use for erectile dysfunction reported an increased risk of glaucoma, with HR decreasing over time (1.38, 1.23 and 1.18 at 1, 3 and 5 years, respectively).[9] This attenuation may reflect discontinuation of the medication or short-term exposure among susceptible individuals. Tadalafil, a long-acting PDE5i, is approved for the treatment of LUTS, a condition typically requiring prolonged, daily therapy compared with its intermittent use for erectile dysfunction. This chronic exposure may exert cumulative effects on aqueous humour dynamics and IOP regulation. In our study, patients receiving tadalafil exhibited a higher susceptibility to developing glaucoma. The increased risk remained evident when outcomes were defined as ocular hypertension, primary open-angle glaucoma or initiation of medical treatment for glaucoma. In contrast, no significant difference was observed in the risk of primary angle-closure glaucoma between tadalafil users and non-PDE5i users. Because the pathogenesis of primary angle-closure glaucoma is primarily related to anatomical narrowing of the anterior chamber angle, and tadalafil is not known to affect iris–lens diaphragm configuration or anterior segment anatomy, its use is unlikely to substantially alter the risk of primary angle-closure glaucoma.[24] Although one case report described an acute angle-closure attack following sildenafil citrate-aided sexual intercourse, the authors speculated that increased choroidal blood flow induced by sildenafil, together with pupil dilation during sexual activity, may have contributed to the event.[25]

PDE5i have been reported to be associated with NAION.[6] It has been proposed that PDE5i-induced systemic hypotension may reduce perfusion at the optic nerve head and, in conjunction with a transient hypercoagulable state, lead to localised ischemia. In addition to case reports, prospective studies have shown that although the absolute risk is low, PDE5i use is associated with a 2.4-fold increase in the risk of developing NAION within 1 month of ingestion.[26] A similar mechanism may also contribute to an increased risk of glaucoma. In individuals with impaired autoregulation of the optic nerve head or retina, the hypotensive effects of PDE5i may cause transient hypoperfusion of the optic nerve. Repeated episodes of hypoperfusion and reperfusion could induce oxidative stress and retinal ganglion cell injury, thereby predisposing individuals to glaucoma or accelerating its progression in those with pre-existing disease.[27] Therefore, an association between PDE5i use and normal-tension glaucoma is mechanistically plausible. However, no significant association was observed between PDE5i use and normal-tension glaucoma in the present study. Because the identification of normal-tension glaucoma relied on ICD-10 diagnostic codes and IOP data were unavailable in the claims-based database, glaucoma subtype classification may have limited sensitivity, potentially reducing the ability to detect a true association between PDE5i use and normal-tension glaucoma.[28] Alpha-blockers, a common first-line treatment for LUTS, may also cause systemic hypotension and potentially reduce optic nerve perfusion pressure. In the present study, alpha-blocker use was balanced between groups through propensity score matching, minimising its potential confounding effect on the observed association.

NO promotes trabecular meshwork relaxation and thereby enhances aqueous humour outflow. Previous studies have shown that NO production is reduced in patients with glaucoma.[29] PDE5i do not participate in the synthesis or release of NO and thus cannot directly compensate for endogenous NO deficiency. Instead, their mechanism of action lies downstream of the NO signalling pathway to amplify the physiological

effects of endogenous NO.[30] In individuals without glaucoma, the NO–cGMP pathway is likely functioning within a normal physiological range. Consequently, any additional benefit of PDE5 inhibition on trabecular meshwork relaxation or IOP reduction may be limited. Therefore, the transient IOP elevation associated with PDE5i-induced vasodilation in the ciliary body may outweigh the potential protective effects of enhanced outflow. However, although an IOP-related mechanism remains biologically plausible, the observational design of the present study cannot confirm an effect on IOP, nor distinguish the contribution of optic nerve hypoperfusion to the observed association. Future studies incorporating concurrent IOP and ocular perfusion measurements are warranted to elucidate the underlying mechanisms.

This study has several limitations. Although we used propensity score matching to balance covariates and minimise confounding, unmeasured variables may still have influenced the results. Only covariates documented before the index date were included in the matching process; therefore, changes in clinical status, medication use or comorbidity burden during follow-up may have affected the outcomes. Differential healthcare utilisation may also have influenced glaucoma ascertainment. Although the increased glaucoma risk among tadalafil users remained significant after additionally matching for prior ophthalmology visits, detection bias cannot be fully excluded, as we were unable to capture all aspects of healthcare utilisation, referral patterns or follow-up intensity. Second, although alpha-blocker monotherapy could have served as an active comparator, we did not adopt this approach because alpha-blockers can cause systemic hypotension and may independently influence ocular perfusion pressure, thereby introducing an additional source of bias. To account for differences in LUTS treatment profiles, concomitant LUTS medications, including alpha-blockers, 5-alpha reductase inhibitors and anticholinergic agents, were incorporated as matching covariates. Nevertheless, residual confounding by treatment indication or treatment eligibility cannot be fully excluded. Given that patients who were not prescribed tadalafil because of poorer cardiovascular health may have had a higher baseline risk of glaucoma, this potential bias would be expected to attenuate rather than exaggerate the observed association. Because TriNetX aggregates data from multiple healthcare organisations, variations in diagnostic coding may exist. Furthermore, as the database is de-identified, individual patient records could not be reviewed to confirm glaucoma diagnosis or to access key ophthalmic parameters such as IOP, retinal nerve fibre layer thickness or visual field results. Therefore, misclassification among glaucoma subtypes, such as ocular hypertension, primary open-angle glaucoma and normal-tension glaucoma, cannot be fully excluded. For this reason, glaucoma was analysed as a composite primary outcome. Additionally, medication adherence could not be verified, as prescription fulfilment and actual drug use were not captured. Moreover, cumulative tadalafil exposure could not be assessed, limiting the evaluation of potential dose–response effects. Given the observational design, our findings suggest an association rather than a causal relationship between PDE5i use and glaucoma. Future studies employing more advanced causal inference approaches, such as target trial emulation or time-varying propensity score methods, are warranted to validate this association. Lastly, the study population consisted predominantly of white individuals, which may limit the generalisability of the findings to other ethnic groups. This underscores the need for further evaluation in more ethnically diverse populations.

In conclusion, tadalafil use for LUTS was associated with a statistically significant but modest increase in glaucoma risk. These findings do not contraindicate tadalafil use but highlight the importance of baseline ophthalmic assessment and regular follow-up, particularly in patients with pre-existing glaucoma, ocular hypertension, a family history of glaucoma, high myopia or those requiring long-term therapy.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involved human participants and was approved by the Institutional Review Board (IRB) of Taichung Veterans General Hospital (TCVGH) (IRB number: CE24430C-1).

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Data availability statement Data may be obtained from a third party and are not publicly available. The data used in this study were obtained from the TriNetX research network.

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REFERENCES

1 Barroso F, Ribeiro JC, Miranda EP. Phosphodiesterase Type 5 Inhibitors and Visual Side Effects: A Narrative Review. *J Ophthalmic Vis Res* 2021;16:248–59.

2 Te AE, Ramaswamy A, Kaplan SA. Medical Therapy for Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. *Urol Clin North Am* 2025;52:595–604.
3 Kloner RA. Cardiovascular effects of the 3 phosphodiesterase-5 inhibitors approved for the treatment of erectile dysfunction. *Circulation* 2004;110:3149–55.
4 Liu W, Antonelli PJ, Dahm P, *et al*. Risk of sudden sensorineural hearing loss in adults using phosphodiesterase type 5 inhibitors: Population-based cohort study. *Pharmacoepidemiol Drug Saf* 2018;27:587–95.
5 Rivasi G, Rafanelli M, Mossello E, *et al*. Drug-Related Orthostatic Hypotension: Beyond Anti-Hypertensive Medications. *Drugs Aging* 2020;37:725–38.
6 Etminan M, Sodhi M, Mikelberg FS, *et al*. Risk of Ocular Adverse Events Associated With Use of Phosphodiesterase 5 Inhibitors in Men in the US. *JAMA Ophthalmol* 2022;140:480–4.
7 Pomeranz HD, Smith KH, Hart WM, *et al*. Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2002;109:584–7.
8 Belladelli F, Li S, Zhang CA, *et al*. Use of phosphodiesterase 5 inhibitors is not associated with ocular adverse events. *J Sex Med* 2023;20:1399–406.
9 Freyaldenhoven KJ, Johnson JA, Lee DJ, *et al*. Risk of Glaucoma in Men Taking Sildenafil: A Propensity-Score-Matched Study. *TNOA J Ophthalmic Sci Res* 2025;63:172–8.
10 Chen SP, Singh K, Lin SC. Use of phosphodiesterase inhibitors and prevalence of self-reported glaucoma in the United States. *PLoS One* 2017;12:e0183388.
11 Gerometta R, Alvarez LJ, Candia OA. Effect of sildenafil citrate on intraocular pressure and blood pressure in human volunteers. *Exp Eye Res* 2011;93:103–7.
12 Cordell WH, Maturi RK, Costigan TM, *et al*. Retinal effects of 6 months of daily use of tadalafil or sildenafil. *Arch Ophthalmol* 2009;127:367–73.
13 Kim DY, Silverman RH, Chan RVP, *et al*. Measurement of choroidal perfusion and thickness following systemic sildenafil (Viagra(®)). *Acta Ophthalmol* 2013;91:183–8.
14 Harris A, Kagemann L, Ehrlich R, *et al*. The effect of sildenafil on ocular blood flow. *Br J Ophthalmol* 2008;92:469–73.
15 Yap TE, Kelada M, Imperial-Ollero JA, *et al*. Phosphodiesterase inhibitors in glaucoma (PhIGS): a prospective OCTA study. *Invest Ophthalmol Vis Sci* 2020;61:630.
16 Newman-Casey PA, Talwar N, Nan B, *et al*. The relationship between components of metabolic syndrome and open-angle glaucoma. *Ophthalmology* 2011;118:1318–26.
17 Wändell P, Carlsson AC, Ljunggren G. Systemic diseases and their association with open-angle glaucoma in the population of Stockholm. *Int Ophthalmol* 2022;42:1481–9.
18 Muayad J, Loya A, Hussain ZS, *et al*. Comparative Effects of Glucagon-like Peptide 1 Receptor Agonists and Metformin on Glaucoma Risk in Patients with Type 2 Diabetes. *Ophthalmology* 2025;132:271–9.
19 Baker JC, Fintelmann R, Sharifi R, *et al*. Precautions and Monitoring of Patients Taking Phosphodiesterase Type 5 Inhibitors Who are at Risk of Increased Intraocular Pressure. *Drugs Aging* 2019;36:991–7.
20 Foresta C, Caretta N, Zuccarello D, *et al*. Expression of the PDE5 enzyme on human retinal tissue: new aspects of PDE5 inhibitors ocular side effects. *Eye (Lond)* 2008;22:144–9.
21 Moschos MM, Nitoda E. Pathophysiology of visual disorders induced by phosphodiesterase inhibitors in the treatment of erectile dysfunction. *Drug Des Devel Ther* 2016;8:3407–13.
22 Cavet ME, Vittitow JL, Impagnatiello F, *et al*. Nitric oxide (NO): an emerging target for the treatment of glaucoma. *Invest Ophthalmol Vis Sci* 2014;55:5005–15.
23 Grunwald JE, Jacob SS, Siu K, *et al*. Acute effects of sldenafil ctrate (Viagra) on intraocular pressure in open-angle glaucoma. *Am J Ophthalmol* 2001;132:872–4.
24 Gani J, Perlis N, Radomski SB. Urologic medications and ophthalmologic side effects: a review. *Can Urol Assoc J* 2012;6:53–8.
25 Ramasamy B, Rowe F, Nayak H, *et al*. Acute angle-closure glaucoma following sildenafil citrate-aided sexual intercourse. *Acta Ophthalmol Scand* 2007;85:229–30.
26 Campbell UB, Walker AM, Gaffney M, *et al*. Acute nonarteritic anterior ischemic optic neuropathy and exposure to phosphodiesterase type 5 inhibitors. *J Sex Med* 2015;12:139–51.
27 Moore D, Harris A, Wudunn D, *et al*. Dysfunctional regulation of ocular blood flow: A risk factor for glaucoma? *Clin Ophthalmol* 2008;2:849–61.
28 Fujita A, Aoyama Y, Yamana H, *et al*. Validity of Algorithms to Identify Patients With Glaucoma Using the Japanese Claims Data. *J Glaucoma* 2023;32:307–12.
29 Wan Y, Guo X, Wang N. Trabecular meshwork: A pivotal target for evolving glaucoma treatments. *Surv Ophthalmol* 2025;70:1043–60.
30 Wareham LK, Buys ES, Sappington RM. The nitric oxide-guanylate cyclase pathway and glaucoma. *Nitric Oxide* 2018;77:75–87.