Is tadalafil associated with decreased risk of major adverse cardiac events or venous thromboembolism in men with lower urinary tract symptoms?

Sankalp Goberdhan1 · Ruben Blachman-Braun2 · Sirpi Nackeeran2 · Thomas A. Masterson 3rd2 · Ranjith Ramasamy2

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Abstract
Purpose To evaluate the association of tadalafil, a phosphodiesterase-5 inhibitor (PDE5I), with major adverse cardiac events (MACE) or venous thromboembolism (VTE) in men with lower urinary tract symptoms (LUTS).
Methods Data was obtained from the TriNetX Research Network, ICD-10 codes were used to identify men with LUTS, MACE, and VTE. In addition, demographic characteristics and use of tadalafil or alpha-blocker was evaluated. Then, unbalanced and balanced association analyses was performed to assess the relation between tadalafil and/or alpha-blocker use with MACE/VTE.
Results After participant selection, analysis included 821,592 men that did not use an alpha blocker or tadalafil, 5,004 men that used tadalafil but no alpha blocker, 327,482 men that used an alpha blocker but no tadalafil, and 6,603 men that used both an alpha blocker and tadalafil. On balanced analysis, tadalafil was independently associated with a decreased risk of MACE/VTE within a 3-year time period (OR = 0.59, 95%CI 0.49–0.70, p < 0.0001). Among men with a history of alpha blocker use, tadalafil use was also independently associated with a decreased risk of MACE or VTE, both before and after controlling for potentially confounding variables (OR = 0.57, 95%CI: 0.50–0.66; p < 0.0001).
Conclusions In our study, tadalafil was associated with a decreased risk of MACE/VTE in men with LUTS with and without a history of alpha blocker use. It is time to perform further long-term prospective randomized studies to further analyze the cardiovascular effects of PDE5Is as combination treatment with alpha blockers in the management of LUTS.

Keywords Lower urinary tract symptoms · Major adverse cardiac events · Venous thromboembolism · A phosphodiesterase-5 inhibitors

Introduction
Cardiac disease and major adverse cardiac events (MACE) are the leading cause of mortality in the US, causing 1 in 4 deaths [1]. Risk factors for a MACE differ between men and women [2]. Men with moderate to severe lower urinary tract symptoms (LUTS) have an increased risk MACE, and the severity of the LUTS correlates to MACE risk [3, 4]. LUTS are a major cause of morbidity in men and are classified as storage, voiding, and post-micturition symptoms. LUTS may be caused by a variety of disease processes but the two most well-known are prostate enlargement and overactive bladder [5]. The pharmacological armamentarium for treating LUTS include six drug classes, used alone or in combination with each other: alpha-adrenoceptor blockers, 5alpha-reductase inhibitors, phytotherapeutics, antimuscarinics, beta3-adrenoceptor agonists, and phosphodiesterase type 5 inhibitors (PDE5I) [6]. First line therapy typically involves prescription of an alpha-blocker; however, alpha blockers are associated with cardiac failure [7, 8]. Of these medications, PDE5I cause vasodilation, which may provide some cardio protection and decrease MACE.
Phosphodiesterase-5 (PDE5) is the enzyme responsible for the breakdown of cyclic guanosine monophosphate (cGMP) in smooth muscle [9]. PDE5Is are structurally similar to cGMP, and competitively bind to PDE5, therefore, increasing cGMP. Increased cGMP causes a decrease in smooth muscle calcium leading to smooth muscle relaxation and in the penis, increased blood flow and erection [9]. Vasodilators, such as hydralazine, nitrates and calcium channel blockers have been used as antihypertensives for decades; however, PDE5Is are not. Interestingly, PDE5I are used for cases of pulmonary hypertension. It is, therefore, possible that the vasodilatory effects of PDE5Is may be cardioprotective in men suffering from LUTS [10]. We hypothesize that men with LUTS taking PDE5Is will have decreased MACE or venous thromboembolism (VTE) events compared to men with LUTS not taking a PDE5I. To test our hypothesis, we analyzed a large sample of men with LUTS using data stored within the TriNetX Research Network, a federated database that complies electronic health record data from healthcare organizations (HCOs) around the United States.

**Methods**

**Data source and study design**

We accessed the TriNetX Research Network for analysis of electronic health record data from 42 HCOs that include information for 67,070,906 patients. TriNetX has received a waiver from the Institutional Review Board and all patient data is de-identified. Instances of medication data are recorded within the database from review of patient charts, orders, and prescriptions written. Diagnoses are categorized by International Classification of Disease, Tenth Revision (ICD-10) codes. Demographic data is obtained from patient chart review.

**Cohorts**

Diagnosis codes used to identify LUTS, MACE, and VTE are identified in Supplementary Table 1. To test the association between tadalafil and MACE/VTE within two groups: men with a history of alpha-blocker use and men without a history of alpha-blocker use. In each group, an analysis was performed comparing men with a history of tadalafil against men without a history of tadalafil use. We assessed a recorded MACE/VTE diagnosis (Supplementary Table 1) within 3 years of index event as our primary outcome. Index event was defined as the point at which a patient was diagnosed with LUTS and, when applicable, recorded to have used tadalafil and/or an alpha-blocker.

We measured association by odds ratios (ORs), which were determined both before and after controlling for confounding variables. Confounding variables were controlled for by 1:1 greedy nearest-neighbor propensity score matching, a statistical technique that uses logistic regression to generate similarly sized cohorts based on variables of interest [11, 12]. We performed comparisons through the TriNetX software, which is powered by R and python, and assessed the adequacy of propensity score match when standardized differences were less than 0.1. Sample sizes following propensity score matching approximated the smaller of the matched samples. A p value < 0.05 was considered statistically significant.

We controlled for the following established risk factors for MACE/VTE: dyslipidemia (E78), diabetes (E08–E13), hypertension (I10), obesity (E66), age, ethnicity, tobacco use (F17), sleep apnea (G47.33), and use of statins (CV350), beta-blockers (CV100), aspirin (1191), clopidogrel (32968), and ACE inhibitors (CV800). We additionally controlled for finasteride or dutasteride use.

**Results**

Among men with a history of LUTS and no history of MACE or VTE within 1 year of their LUTS diagnosis, we identified 821,592 patients who did not use an alpha blocker or tadalafil, 5,004 patients who used tadalafil but no alpha blocker, 327,482 patients who used an alpha blocker but no tadalafil, and 6,603 patients who used both an alpha blocker and tadalafil (Table 1). Within the group of men who did not have history of alpha blocker use, the group that used tadalafil was significantly more likely to have cardiovascular risk factors, including older age and higher rates of having or taking a medication for a lipid disorder, diabetes, hypertension, or ischemic heart disease. Among men with a history of taking an alpha blocker, those who used tadalafil were more likely to have or take...
a medication for lipid disorders or hypertension, but less likely to have ischemic heart disease or diabetes.

Prior to balancing for confounding variables through propensity score matching, tadalafil was not significantly associated with MACE/VTE in the group of men without a history of alpha blocker use (OR = 1.13, 95% CI 0.99–1.30; \( p = 0.0757 \), Table 2A). However, once adjusting for potential cardiovascular risk factors, tadalafil was independently associated with a decreased risk of MACE/VTE within a 3-year time period (OR = 0.59, 95%CI 0.49–0.70; \( p < 0.0001 \), Table 2A). Among men with a history of alpha blocker use, tadalafil use was also independently associated with a decreased risk of MACE or VTE, both before and after controlling for potentially confounding variables (OR = 0.57, 95%CI 0.50–0.66; \( p < 0.0001 \), Table 2B).

### Discussion

Though a well-known vasodilatory agent, it was unknown if the PDE5I tadalafil affects the incidence rate of MACE/VTEs in men with BPH. To answer this question, we conducted an analysis of the TriNetX Research Network, looking at men with a history of LUTS with a history of taking tadalafil, alpha blockers, combo tadalafil-alpha-blocker therapy, or neither. After controlling for potentially confounding variables during statistical analysis, such as comorbidities, age, ethnicity, medication use, tadalafil was shown to significantly decrease

### Table 1 Baseline population characteristics

| Variable                  | No alpha blocker or tadalafil | Tadalafil, no alpha blocker | \( p \) value | Alpha blocker, no tadalafil | Alpha blocker and tadalafil | \( p \) value |
|---------------------------|-------------------------------|----------------------------|--------------|-----------------------------|-----------------------------|--------------|
| Number in cohort          | 821,592                       | 5004                       | –            | 327,482                     | 6,603                       | –            |
| Age (years)               | 42.8 ± 25.7                   | 59.6 ± 12.1                | < 0.0001     | 63.8 ± 16.2                 | 64.4 ± 10.5                 | 0.0005       |
| Race                      |                               |                            |              |                             |                             |              |
| White                     | 67%                           | 74%                        | < 0.0001     | 76%                         | 78%                         | 0.0293       |
| Black                     | 15%                           | 13%                        | < 0.0001     | 10%                         | 11%                         | 0.0160       |
| Asian                     | 2%                            | 1%                         | < 0.0001     | 2%                          | 2%                          | 0.0002       |
| Native American           | < 1%                          | < 1%                       | –            | < 1%                        | < 1%                        | –            |
| Unknown                   | 15%                           | 11%                        | < 0.0001     | 11%                         | 10%                         | 0.0026       |
| Ethnicity                 |                               |                            |              |                             |                             |              |
| Hispanic                  | 9%                            | 5%                         | < 0.0001     | 6%                          | 4%                          | < 0.0001     |
| Not Hispanic              | 52%                           | 65%                        | < 0.0001     | 62%                         | 70%                         | < 0.0001     |
| Unknown                   | 39%                           | 31%                        | < 0.0001     | 31%                         | 25%                         | < 0.0001     |
| Lipid disorders (E78)     | 17%                           | 44%                        | < 0.0001     | 39%                         | 49%                         | < 0.0001     |
| Diabetes Mellitus (E08–E13)| 9%                           | 17%                        | < 0.0001     | 21%                         | 19%                         | 0.0021       |
| Essential hypertension (I10)| 20%                         | 43%                        | < 0.0001     | 46%                         | 51%                         | < 0.0001     |
| Overweight and Obesity (E66)| 6%                           | 14%                        | < 0.0001     | 13%                         | 16%                         | < 0.0001     |
| Ischemic heart diseases (I20–I25)| 6%             | 11%                        | < 0.0001     | 18%                         | 16%                         | < 0.0001     |
| Cerebral infarction (I63) | 0%                            | 1%                         | 0.0227       | 2%                          | 1%                          | < 0.0001     |
| Sleep apnea (G47.3)       | 5%                            | 13%                        | < 0.0001     | 11%                         | 16%                         | < 0.0001     |
| Nicotine Use (Z87.891)    | 4%                            | 8%                         | < 0.0001     | 13%                         | 13%                         | 0.2658       |
| Antilipemic agents        | 11%                           | 36%                        | < 0.0001     | 34%                         | 47%                         | < 0.0001     |
| Beta blockers             | 9%                            | 24%                        | < 0.0001     | 29%                         | 32%                         | < 0.0001     |
| ACE inhibitors            | 8%                            | 20%                        | < 0.0001     | 22%                         | 26%                         | < 0.0001     |
| Aspirin                   | 9%                            | 22%                        | < 0.0001     | 26%                         | 31%                         | < 0.0001     |
| Clopidogrel               | 1%                            | 3%                         | < 0.0001     | 6%                          | 5%                          | 0.093        |
| Finasteride or dutasteride| 1%                            | 5%                         | < 0.0001     | 9%                          | 23%                         | < 0.0001     |

### Table 2 Odds ratios for MACE/VTE events among men with LUTS based on medication use

| Comparison                                         | Unbalanced OR (95% CI) | Balanced OR (95% CI) |
|----------------------------------------------------|------------------------|----------------------|
| (A) Tadalafil alone vs no tadalafil or alpha blockade | 1.13 (0.99–1.30) \( p = 0.0757 \) | 0.59 (0.49–0.70) \( p < 0.0001 \) |
| (B) Alpha blockade and tadalafil vs alpha blockade without tadalafil | 0.56 (0.50–0.63), \( p < 0.0001 \) | 0.57 (0.50–0.66) \( p < 0.0001 \) |
the incidence rate of MACE/VTEs in men with a history of LUTS without a history of alpha-blocker use (OR = 0.59, 95% CI 0.49–0.70; p < 0.0001, Table 2A). Patients with a history of alpha-blocker use had risk (OR = 0.57, 95% CI 0.50–0.66, p < 0.0001, Table 2B) of experiencing a MACE/VTE before and after controlling for potentially confounding variables. Alpha-blocker use alone has been first line to treat LUTS; maybe tadalafil can be added as a first line combination therapy due to its efficacy for treating LUTS, decreased odds of MACE/VTE occurrence, and decreased side effect profile [13].

The International Prostate Symptom Score is used to describe the severity of LUTS and is often used to compare the efficacy of different medications used to treat LUTS. Tadalafil by itself has been shown to lower IPSS total score, voiding subscore, and storage subscore in men ≥ 40 years [14]. Several studies have shown that combination therapy of PDE5I’s and alpha blockers work better than either drug alone in managing LUTS due to BPH [15, 16]. The order of drug administration does not have any significant effects [17]. A meta-analysis suggests that sildenafil–tamsulosin is a reliable combination therapy for men with LUTS with/without ED [18]. Further studies are required to compare tadalafil vs sildenafil in combination with tamsulosin on LUTS improvement. First line therapy has traditionally been to use an alpha blocker, but that may not be enough [8]. It has been shown that men with LUTS due to BPH resistant to alpha blocker treatment had significant improvements in their IPSS scores when later treated with tadalafil, and vice versa [17, 19].

Tadalafil has been reported not to increase the risk of cardiovascular treatment-emergent adverse effects in men with LUTS [20]. Our study has shown that use of tadalafil is associated with decreased risk of MACE/VTE occurring in men with LUTS. Despite the well known potential erectile and cardiovascular benefits associated with tadalafil, clinicians should also take into consideration the potential side effects including mild-to-moderate headache, flushing, and dyspepsia [21]. In comparison, alpha-blocker nonsexual side effects include cardiovascular effects, such as postural hypotension, asthenia, and dizziness, as well as idiopathic floppy iris syndrome [8, 22]. Alpha blocker use has been shown to decrease relative risk of mortality from COVID-19, while further investigation on PDE5Is effect on COVID-19 outcomes is needed [23].

Additional benefits of adding tadalafil to standard LUTS treatment include its sexual benefits and recent decrease in price. Tadalafil is a known erectile disfunction drug, tolerated well by many [24]. PDE5I use has demonstrated a potential increase in sperm motility and morphology [25]. Of the popular PDE5Is, some patients prefer tadalafil over sildenafil for treatment of erectile dysfunction, possibly because of its longer duration of effect as it has the longest half-life (17.5 h.) of the commonly used PDE5Is tadalafil, sildenafil, and vardenafil [26, 27]. PDE5I use is not limited to LUTS and sexual dysfunction; in combination with other drugs, they are used successfully to treat pulmonary artery hypertension [28]. Tadalafil is now more accessible than ever; it became a generic drug when its patent expired in November 2017, leading to a 49% decrease in cost per unit [29]. The safety profiles of the generic drug and marketed drug are similar [30].

As with all studies, ours is not without its own strengths and limitations. Our analysis relies on data recorded in electronic medical records and is, therefore, prone to errors of incorrect coding or incomplete documentation. Furthermore, we did not have access to information regarding socioeconomic status, severity of LUTS, medication adherence, or lifestyle factors. We additionally had to refrain from excluding all patients without a follow-up visit, as this might have excluded patients with the outcome of interest. This study is strengthened by the large sample size, our ability to control for potentially confounding variables through propensity score matching, adjustment for immortal bias through precise time window specifications, and information regarding chronology of diagnoses.

In our study tadalafil was associated with decreased risk of MACE/VTE in men with LUTS with and without a history of alpha blocker use. Alpha blockers are the traditional first line drug in the treatment of LUTS; however, considering adding tadalafil for the treatment of LUTS might provide a cardiovascular benefit. It is time to perform long-term prospective randomized studies to further analyzing the cardiovascular effect PDE5Is as combination treatment in the management of LUTS.

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Ethical approval Ethical approval was waived by the local Ethics Committee of University of Miami in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.
References

1. Virani SS, Alonso A, Benjamin EJ et al (2020) Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation 141(9):e139–e596. https://doi.org/10.1161/cir.0000000000000757

2. Andersen KK, Andersen ZJ, Olsen TS (2010) Age- and gender-specific prevalence of cardiovascular risk factors in 40,102 patients with first-ever ischemic stroke: a Nationwide Danish Study. Stroke 41(12):2768–2774. https://doi.org/10.1161/strokeaha.110.597585

3. Gacci M, Corona G, Sebastianelli A et al (2016) Male lower urinary tract symptoms and cardiovascular events: a systematic review and meta-analysis. Eur Urol 70(5):788–796. https://doi.org/10.1016/j.eururo.2016.07.007

4. Russo GI, Castelli T, Privitera S et al (2015) Increase of Framingham cardiovascular disease risk score is associated with severity of lower urinary tract symptoms. BJU Int 116(5):791–796. https://doi.org/10.1111/bju.13053

5. Abrams P, Cardozo L, Fall M et al (2003) The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 61(1):37–49. https://doi.org/10.1001/s0090-4295(02)02243-4

6. De Nunzio C, Pesicce F, Tubaro A (2016) Combination therapies for improved management of lower urinary tract symptoms/benign prostatic hyperplasia. Drugs Today (Barc) 52(9):501–517. https://doi.org/10.1358/dt.2016.52.9.2525739

7. Lepor H (2016) Alpha-blockers for the treatment of benign prostatic hyperplasia. Urol Clin North Am 43(3):313–323. https://doi.org/10.1016/j.ucr.2016.04.009

8. Huang SA, Lie JD (2013) Phosphodiesterase-5 (PDE5) inhibitors in the management of erectile dysfunction. P1 238(7):407–419

9. Nickel JC (2021) Cardiac failure associated with medical therapy for improved management of lower urinary tract symptoms/benign prostatic hyperplasia related symptoms: a randomized double (2019) Efficacy of tamsulosin and tadalafil in relieving benign prostatic hyperplasia type 5 inhibitors with tamsulosin for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia with or without erectile dysfunction: a network meta-analysis. Biomed Res Int 2020:1419520. https://doi.org/10.1155/2020/1419520

10. Takahashi R, Miyazato M, Nishii H et al (2018) Tadalafil for male lower urinary tract symptoms improves endothelial function. Int J Urol 24(3):206–210. https://doi.org/10.1111/iju.13273

11. Wang Y, Bao Y, Liu J, Duan L, Cui Y (2018) Tadalafil 5 mg once daily improves lower urinary tract symptoms and erectile function. Int J Urol 122(7):652–657. https://doi.org/10.1097/01.iju.000012857.39680.ce

12. Yuan J, Zhang R, Yang Z et al (2013) Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol 65(3):902–912. https://doi.org/10.1016/j.eururo.2013.01.012

13. Tan P, Liu L, Wei S, Tang Z, Yang L, Wei Q (2017) The effect of alpha-1 adrenergic receptor antagonists and in-hospital mortality from COVID-19. Front Med (Lausanne) 8:637647. https://doi.org/10.3389/fmed.2021.637647

14. Yue J, Zhang R, Yang Z et al (2013) Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol 65(3):902–912. https://doi.org/10.1016/j.eururo.2013.01.012

15. Tang J, Long J, Yang L, Wei Q (2017) The effect of alpha phosphodiesterase-5 inhibitors on sperm parameters: a meta-analysis and systematic review. Urology 105:54–61. https://doi.org/10.1016/j.urology.2017.02.032

16. Doggrell SA (2005) Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. Expert Opin Pharmacother 6(1):75–84. https://doi.org/10.1517/14656566.6.1.75

17. Ramakrishna NV, Vishwotam KN, Puran S et al (2004) Quantitation of tadalafil in human plasma by liquid chromatography-tandem mass spectrometry with electrospray ionization. J Chromatogr B 809(2):243–249. https://doi.org/10.1016/j.jchromb.2004.06.026

18. Fu W, He W, Li Y et al (2021) Efficacy and safety of novel-targeted drugs in the treatment of pulmonary arterial hypertension: a Bayesian network meta-analysis. Drug Deliv 28(1):1007–1019. https://doi.org/10.1080/10777317.2020.1927243

19. Bell C, Hadi MA, Khanal S, Paudyal V (2021) Prescribing patterns and costs associated with erectile dysfunction drugs in England: a time trend analysis. BJGP Open. https://doi.org/10.3399/bjgpopen20X101145

20. Shao R, Yang DD, Ruan ZR et al (2021) Pharmacokinetic and bioequivalence evaluation of 2 tadalafil tablets in healthy male chinese subjects under fasting and fed conditions. Clin Pharmacol Drug Dev. https://doi.org/10.1002/cpdd.1007

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