

Association of daily and on-demand tadalafil use with all-cause mortality and cardiovascular outcomes in men with erectile dysfunction and lower urinary tract symptoms: a propensity score-matched real-world cohort study

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Abstract

Background

Erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia are common conditions in middle-aged and older men and are associated with an increased risk of cardiovascular disease and mortality. Emerging evidence suggests that phosphodiesterase type 5 (PDE5) inhibitors may provide cardiovascular benefits beyond symptomatic improvement. Tadalafil is unique among PDE5 inhibitors because it is prescribed as either a once-daily low-dose regimen (5 mg) or an on-demand high-dose regimen (20 mg). However, whether these dosing strategies differ in their association with long-term mortality and cardiovascular outcomes remains uncertain. This study evaluated the association of daily tadalafil 5 mg and on-demand tadalafil 20 mg use with all-cause mortality and cardiovascular outcomes in men with ED and/or LUTS.

Methods

This retrospective cohort study used de-identified electronic health record data from the TriNetX US Collaborative Network. Men aged ≥ 40 years diagnosed with ED and/or LUTS between January 2012 and December 2022 who received tadalafil 5 mg or tadalafil 20 mg were identified and compared with patients who did not receive PDE5 inhibitors. Patients with pre-existing major cardiovascular disease, exposure to other PDE5 inhibitors, or receipt of both tadalafil regimens were excluded. A two-phase analysis was performed, comparing each tadalafil regimen with non-users, followed by a direct comparison between tadalafil 5 mg and tadalafil 20 mg. Propensity score matching was performed for demographic characteristics and major comorbidities. The primary outcomes were all-cause mortality, cerebrovascular accident, heart failure, and ischaemic heart disease in the period of 14 years of follow-up.

Results

The final study population included 28,376 patients receiving tadalafil 5 mg, 31,321 receiving tadalafil 20 mg, and 1,066,587 patients who did not receive PDE5 inhibitors. After propensity score matching, both tadalafil 5 mg and tadalafil 20 mg were associated with significantly lower risks of all-cause mortality (risk ratio [RR] 0.574 and 0.617, respectively), cerebrovascular accident (RR 0.727 and 0.818), heart failure (RR 0.668 and 0.704), and ischaemic heart disease (RR 0.819 and 0.856) compared with non-users. In the propensity score-matched head-to-head comparison, Kaplan–Meier analyses demonstrated improved overall survival (HR 1.116, 95% CI 1.033–1.205; $P = 0.005$) and cardiovascular disease-free survival (HR 1.050, 95% CI 1.010–1.091; $P = 0.013$) among patients receiving tadalafil 20 mg compared with tadalafil 5 mg.

Conclusions

Among men aged ≥ 40 years with ED and/or LUTS, treatment with either tadalafil 5 mg or tadalafil 20 mg was associated with lower risks of all-cause mortality and individual cardiovascular outcomes compared

with non-use of PDE5 inhibitors. In this observational study, on-demand tadalafil 20 mg was associated with more favourable long-term survival outcomes than daily tadalafil 5 mg in time-to-event analyses. Prospective randomized studies are warranted to confirm these findings and determine whether the observed associations reflect a causal treatment effect.

(Clinical trial number: not applicable)

INTRODUCTION

Erectile dysfunction (ED) is one of the most prevalent chronic conditions affecting men, with an estimated prevalence of up to 52% among those aged over 40 years. Beyond its detrimental effects on quality of life, sexual function, and interpersonal relationships, ED is increasingly recognised as an early clinical manifestation of systemic vascular disease. Endothelial dysfunction, impaired nitric oxide bioavailability, chronic inflammation, and atherosclerosis represent common pathophysiological mechanisms linking ED with cardiovascular disease (CVD), and the onset of ED frequently precedes individual cardiovascular outcomes by several years. Consequently, ED is now regarded not only as a sexual disorder but also as an important marker of future cardiovascular risk. [1, 2, 3, 4, 5]

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) are another common condition affecting ageing men and often coexist with ED. Epidemiological studies have demonstrated a strong association between LUTS and ED, with both disorders sharing common risk factors including ageing, hypertension, diabetes mellitus, obesity, metabolic syndrome, and endothelial dysfunction. The coexistence of ED and LUTS is associated with poorer quality of life and increased healthcare utilisation, highlighting the importance of treatment strategies that address both conditions simultaneously. [6, 7]

Phosphodiesterase type 5 (PDE5) inhibitors remain the first-line pharmacological treatment for ED. Among the available agents, tadalafil possesses several pharmacokinetic and clinical advantages, including a prolonged elimination half-life of approximately 17.5 hours, sustained therapeutic efficacy, and absorption that is unaffected by food intake. These characteristics permit flexible dosing either as a once-daily low-dose regimen (5 mg) or as an on-demand higher-dose regimen (20 mg). Furthermore, tadalafil 5 mg once daily is the only PDE5 inhibitor approved by the United States Food and Drug Administration for the treatment of both ED and LUTS secondary to BPH, making it a unique therapeutic option for men with these frequently coexisting conditions. [8, 6, 9]

Beyond symptomatic improvement, increasing evidence suggests that PDE5 inhibitors may exert favourable cardiovascular effects through mechanisms extending beyond penile smooth muscle relaxation. Inhibition of PDE5 enhances nitric oxide–cyclic guanosine monophosphate signalling, resulting in improved endothelial function, vasodilation, reduced vascular stiffness, inhibition of platelet aggregation, attenuation of inflammatory pathways, and favourable effects on myocardial and vascular remodelling. These pleiotropic effects have led to the successful use of tadalafil in pulmonary arterial

hypertension and have generated growing interest in the potential role of PDE5 inhibitors in reducing cardiovascular morbidity and mortality. [10, 7, 11, 12]

Observational studies and recent systematic reviews have reported associations between PDE5 inhibitor use and reductions in all-cause mortality, major adverse cardiovascular events, heart failure, and stroke among men with ED and other cardiovascular risk factors. [13, 14, 15, 16, 17] However, most published studies have evaluated PDE5 inhibitors as a drug class or have compared users with non-users, without distinguishing between different tadalafil dosing regimens. Although daily tadalafil 5 mg and on-demand tadalafil 20 mg are both widely prescribed in routine clinical practice, whether these treatment strategies differ in their association with long-term mortality and cardiovascular outcomes remains uncertain. Clarifying these potential differences is clinically relevant because treatment selection is frequently influenced by patient characteristics, symptom severity, treatment preferences, and the presence of concomitant LUTS.

Using a large multicentre real-world database, we conducted a retrospective cohort study to evaluate the association of daily tadalafil 5 mg and on-demand tadalafil 20 mg with all-cause mortality and major cardiovascular outcomes in men aged 40 years or older with ED and/or LUTS. We first compared each tadalafil regimen with patients who did not receive PDE5 inhibitors and subsequently performed a direct comparison between the two tadalafil dosing strategies after propensity score matching. We hypothesised that treatment with tadalafil would be associated with lower risks of mortality and cardiovascular events and sought to determine whether differences existed between daily and on-demand tadalafil therapy.

METHODS

Study design and data source

This retrospective cohort study was conducted using data from the TriNetX Research Network (TriNetX LLC, Cambridge, MA, USA), a global federated health research platform that provides access to de-identified electronic health records from participating healthcare organisations. The database includes routinely collected demographic information, diagnoses, procedures, medications, laboratory investigations, and mortality data from multiple healthcare systems. [18]

Data were obtained from the TriNetX US Collaborative Network, which comprises 71 healthcare organisations and includes electronic health records from more than 50 million adult male patients. Data were accessed between **August 2025 and December 2025**. The TriNetX platform complies with the Health Insurance Portability and Accountability Act (HIPAA) and the General Data Protection Regulation (GDPR), ensuring that all patient information is de-identified before analysis. Because only anonymised data were analysed, no identifiable patient information was available to the investigators.

Study population

Male patients aged ≥ 40 years with a diagnosis of erectile dysfunction (ED) and/or lower urinary tract symptoms (LUTS) between 1 January 2012 and 31 December 2022 were eligible for inclusion.

ED was identified using the International Classification of Diseases, Tenth Revision (ICD-10) code N52. LUTS was defined as benign prostatic hyperplasia with lower urinary tract symptoms (ICD-10 code N40.1) or nodular prostate with lower urinary tract symptoms (ICD-10 code N40.3).

Patients who received tadalafil within six months after the qualifying ED and/or LUTS diagnosis were identified. For the treatment cohorts, the index date was defined as the date of the first tadalafil prescription within this six-month exposure window. Individuals with pre-existing cardiovascular disease, including acute myocardial infarction (ICD-10 code I21), heart failure (ICD-10 code I50), cerebral infarction (ICD-10 code I63), or angina pectoris (ICD-10 code I20), before the index date were excluded to minimise baseline cardiovascular risk.

Patients who had received sildenafil, vardenafil, avanafil, or both tadalafil 5 mg and tadalafil 20 mg during the study period were excluded to minimise treatment crossover and exposure misclassification. Patients with incomplete demographic information required for propensity score matching were also excluded.

Exposure groups

A two-stage analytical strategy was performed.

In the primary analysis, patients prescribed tadalafil 5 mg once daily and those prescribed tadalafil 20 mg on demand were each compared separately with patients diagnosed with ED and/or LUTS who had not received any phosphodiesterase type 5 (PDE5) inhibitor. Patients in the control cohort had no recorded prescription for tadalafil, sildenafil, vardenafil, or avanafil during the study period.

The secondary analysis consisted of a direct comparison between patients receiving tadalafil 5 mg and those receiving tadalafil 20 mg to evaluate differences in mortality and cardiovascular outcomes between the two treatment regimens.

The index date was defined as the date of the first tadalafil prescription for the treatment groups and the corresponding diagnosis date for the control cohort.

Outcome measures

The primary outcome was all-cause mortality.

Secondary outcomes included acute myocardial infarction, heart failure, cerebral infarction, and ischaemic heart disease, which were analysed individually. Cardiovascular disease-free survival was defined as the time from the index date to the first occurrence of acute myocardial infarction (ICD-10

code I21), heart failure (ICD-10 code I50), cerebral infarction (ICD-10 code I63), angina pectoris (ICD-10 code I20), or all-cause mortality.

Patients were followed from the index date until the occurrence of an outcome event, death, loss to follow-up, or the end of the study period, with a maximum follow-up of 14 years.

Propensity score matching

To minimise baseline differences between treatment groups, propensity score matching (PSM) was performed using the built-in TriNetX analytics platform. Patients were matched using a 1:1 greedy nearest-neighbour algorithm without replacement with a caliper width of 0.10 applied to randomly ordered patient records.

The propensity score was estimated using demographic characteristics, including age, race, and ethnicity, together with clinically relevant baseline comorbidities, including hypertension, diabetes mellitus, chronic kidney disease, overweight or obesity, ischaemic heart disease, and cerebrovascular disease. Covariate balance between matched cohorts was assessed using standardised mean differences (SMDs), with an absolute SMD of < 0.10 considered indicative of adequate balance.

Statistical analysis

Continuous variables are presented as means $\pm$ standard deviations, whereas categorical variables are expressed as frequencies and percentages. Baseline characteristics were compared using independent-samples *t*-tests for continuous variables and chi-square tests for categorical variables.

Binary outcomes were compared using risk ratios (RRs) with corresponding 95% confidence intervals (CIs). Time-to-event outcomes were analysed using Kaplan–Meier survival curves and compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals were generated by the TriNetX analytics platform for survival analyses.

All statistical tests were two-sided, and a *P* value < 0.05 was considered statistically significant. Statistical analyses were performed using the TriNetX analytics platform.

RESULTS

Study population

Between 1 January 2012 and 31 December 2022, a total of 2,070,812 men with erectile dysfunction (ED) and/or lower urinary tract symptoms (LUTS) were identified within the TriNetX US Collaborative Network. After applying the predefined inclusion and exclusion criteria, 1,241,865 men aged ≥ 40 years were eligible for analysis. Of these, 115,581 patients were excluded because of incomplete demographic data required for propensity score matching.

The final study cohort comprised 1,126,284 patients, including 28,376 (2.5%) who received tadalafil 5 mg once daily, 31,321 (2.8%) who received tadalafil 20 mg on demand, and 1,066,587 (94.7%) who did not receive a phosphodiesterase type 5 (PDE5) inhibitor.

The study selection process is illustrated in Fig. 1.

Baseline characteristics

Baseline demographic and clinical characteristics of the study population before propensity score matching are summarized in Table 1.

Patients receiving tadalafil were younger than those who did not receive PDE5 inhibitors. Differences were also observed in race, ethnicity, and the prevalence of several baseline comorbidities, including hypertension, diabetes mellitus, chronic kidney disease, overweight or obesity, ischaemic heart disease, and cerebrovascular disease.

These baseline imbalances justified the use of propensity score matching to improve comparability between treatment groups.

Table 1

Baseline demographic and clinical characteristics of patients receiving tadalafil 5 mg, tadalafil 20 mg, and no PDE5 inhibitor before propensity score matching.

Age at index, years	Tadalafil 5mg n = 28,376	Tadalafil 20mg n = 31,321	No tadalafil n = 1,066,587
	59.1 +/- 10.1*	58.2 +/- 9.7*	65.8 +/- 12.2
Male Gender, n (%)	28,376 (100%)	31,321 (100%)	1,066,587 (100%)
Race or ethnicity, n (%)			
White	21,901 (77%)*	22,627 (72.2%)*	783,504 (73.5%)
American Indian or Alaska Native	100 (0.4%)	84 (0.3%)	3,382 (0.3%)
Native Hawaiian or Other Pacific Islander	72 (0.3%)*	94 (0.3%)*	8,743 (0.8%)
Not Hispanic or Latino	21,103 (74.4%)*	21,966 (70.1%)	749,810 (70.3%)
Hispanic or Latino	1,506 (5.3%)*	1,495 (4.8%)*	71,669 (6.7%)
Black or African American	3,001 (10.6%)	5,235 (16.7%)*	116,207 (10.9%)
Asian	703 (2.5%)*	746 (2.4%)*	45,609 (4.3%)
Unknown Ethnicity	5,767 (20.3%)*	7,860 (25.1%)*	245,108 (23.0%)
Other Race/Unknown Race	848 (3.0%)*	820 (2.6%)*	36,982 (3.5%)
Comorbidities, n (%)			
Hypertension	11,306 (39.8%)	13,046 (41.7%)*	427,448 (40.1%)
Acute /Chronic kidney disease	1,657 (5.8%)*	1,718 (5.5%)*	98,008 (9.2%)
Overweight and obesity	4,039 (14.2%)*	4,647 (14.8%)*	114,768 (10.8%)
Diabetes Mellitus	3,959 (14.0%)*	5,255 (16.8%)	177,285 (16.6%)
Ischemic heart disease	2,272 (8.0%)*	2,234 (7.1%)*	109,593 (10.3%)
Cerebrovascular disease	698 (2.5%)*	655 (2.1%)*	43,260 (4.1%)

Mortality and cardiovascular outcomes

The associations between tadalafil treatment and clinical outcomes before and after propensity score matching are presented in Table 2.

After propensity score matching, both tadalafil regimens were associated with significantly lower risks of all-cause mortality and cardiovascular events compared with patients who did not receive PDE5 inhibitors.

Compared with non-users, tadalafil 5 mg was associated with reduced risks of:

- all-cause mortality (RR 0.574, 95% CI 0.535–0.615),
- cerebrovascular accident (RR 0.727, 95% CI 0.680–0.772),
- heart failure (RR 0.668, 95% CI 0.627–0.713), and
- ischaemic heart disease (RR 0.819, 95% CI 0.785–0.854).

Similarly, tadalafil 20 mg was associated with reduced risks of:

- all-cause mortality (RR 0.617, 95% CI 0.578–0.659),
- cerebrovascular accident (RR 0.818, 95% CI 0.773–0.865),
- heart failure (RR 0.704, 95% CI 0.663–0.748), and
- ischaemic heart disease (RR 0.856, 95% CI 0.822–0.891).

Comparable findings were observed in the unmatched analyses, although stronger associations were evident before propensity score matching, reflecting baseline differences between study groups.

The associations between tadalafil use and clinical outcomes before and after propensity score matching are presented in Table 2.

Following propensity score matching, both tadalafil regimens were associated with significantly lower risks of all-cause mortality and cardiovascular events compared with patients who did not receive PDE5 inhibitors. Patients receiving tadalafil 5 mg had a lower risk of all-cause mortality (RR 0.574, 95% CI 0.535–0.615), cerebrovascular accident (RR 0.727, 95% CI 0.680–0.772), heart failure (RR 0.668, 95% CI 0.627–0.713), and ischaemic heart disease (RR 0.819, 95% CI 0.785–0.854). Similarly, tadalafil 20 mg was associated with reduced risks of all-cause mortality (RR 0.617, 95% CI 0.578–0.659), cerebrovascular accident (RR 0.818, 95% CI 0.773–0.865), heart failure (RR 0.704, 95% CI 0.663–0.748), and ischaemic heart disease (RR 0.856, 95% CI 0.822–0.891) compared with non-users.

Consistent findings were observed in the unmatched analyses, although the magnitude of the associations was greater before propensity score matching, reflecting baseline differences between treatment groups.

Table 2

Risk ratios for all-cause mortality and cardiovascular outcomes before and after propensity score matching.

Outcomes	Risk ratio (95% CI) before Propensity Score Matching		
	5mg vs no tadalafil	20mg vs no tadalafil	5mg vs 20mg
Mortality	0.333 (0.316–0.351)	0.340(0.324–0.358)	0.999 (0.928–1.075)
CVA	0.583 (0.558–0.609)	0.619(0.594–0.646)	1.019(0.610–1.081)
Heart Failure	0.473 (0.451–0.496)	0.490(0.468–0.513)	1.004(0.941–1.072)
Ischemic heart disease	0.718 (0.697–0.740)	0.723(0.703–0.745)	0.992(0.953–1.033)
Outcomes	Risk ratio (95% CI) after Propensity Score Matching		
	5mg vs no tadalafil	20mg vs no tadalafil	5mg vs 20mg
Mortality	0.574(0.535–0.615)	0.617(0.578–0.659)	0.964 (0.889–1.004)
CVA	0.727(0.680–0.772)	0.818(0.773–0.865)	0.942 (0.885–1.004)
Heart Failure	0.668(0.627–0.713)	0.704(0.663–0.748)	1.023 (0.954–1.097)
Ischemic heart disease	0.819(0.785–0.854)	0.856(0.822–0.891)	0.991 (0.949–1.034)

Kaplan–Meier survival analyses

Kaplan–Meier survival analyses demonstrated significantly improved overall survival and cardiovascular disease-free survival among patients receiving tadalafil compared with patients who did not receive PDE5 inhibitors after propensity score matching (Fig. 2).

In the direct comparison between tadalafil dosing regimens, Kaplan–Meier analyses demonstrated significantly better survival outcomes among patients receiving tadalafil 20 mg than among those receiving tadalafil 5 mg (Fig. 3).

For all-cause mortality, the hazard was significantly lower in the tadalafil 20 mg group than in the tadalafil 5 mg group (HR 1.116, 95% CI 1.033–1.205; log-rank $P = 0.005$).

Similarly, tadalafil 20 mg was associated with improved cardiovascular disease-free survival compared with tadalafil 5 mg (HR 1.050, 95% CI 1.010–1.091; log-rank $P = 0.013$).

Although the propensity score-matched risk ratio analyses demonstrated broadly comparable cumulative event rates between the two tadalafil regimens (Table 2), the time-to-event analyses demonstrated significant differences favouring tadalafil 20 mg. These findings suggest that differences between treatment groups became more apparent when the timing of clinical events was taken into account.

Table 3. Kaplan–Meier survival analyses comparing tadalafil 20 mg and tadalafil 5 mg after propensity score matching

Outcome	Hazard Ratio (95% CI)*	Log-rank P value	Interpretation
Overall survival	1.116 (1.033–1.205)	0.005	Tadalafil 20 mg was associated with significantly better overall survival than tadalafil 5 mg.
Cardiovascular disease-free survival†	1.050 (1.010–1.091)	0.013	Tadalafil 20 mg was associated with significantly better cardiovascular disease-free survival than tadalafil 5 mg.

Abbreviations: CI, confidence interval; HR, hazard ratio.

* Hazard ratios are reported with **tadalafil 5 mg as the reference group**. Therefore, an HR >1 indicates a higher hazard among patients receiving tadalafil 5 mg and consequently more favourable survival among patients receiving tadalafil 20 mg.

† Cardiovascular disease-free survival was defined as the time from the index date to the first occurrence of acute myocardial infarction (ICD-10 I21), heart failure (ICD-10 I50), cerebral infarction (ICD-10 I63), angina pectoris (ICD-10 I20), or all-cause mortality.

In the propensity score-matched comparison between tadalafil dosing regimens, Kaplan–Meier survival analyses demonstrated significantly improved overall survival and cardiovascular disease-free survival among patients receiving tadalafil 20 mg compared with tadalafil 5 mg (Figure 3 and **Table 3**). Patients treated with tadalafil 20 mg had a significantly lower hazard of all-cause mortality (HR 1.116, 95% CI 1.033–1.205; log-rank *P* = 0.005) and the composite cardiovascular outcome (HR 1.050, 95% CI 1.010–1.091; log-rank *P* = 0.013).

DISCUSSION

Principal findings

This large real-world retrospective cohort study demonstrated that both tadalafil 5 mg once daily and tadalafil 20 mg on demand were associated with significantly lower risks of all-cause mortality and individual cardiovascular outcomes compared with non-use of phosphodiesterase type 5 (PDE5) inhibitors in men aged ≥40 years with erectile dysfunction (ED) and/or lower urinary tract symptoms (LUTS). These associations remained significant after propensity score matching for demographic characteristics and major cardiovascular comorbidities, suggesting that the observed benefits were unlikely to be explained solely by baseline differences between treatment groups.

A further novel finding of this study was the direct comparison between the two commonly prescribed tadalafil regimens. Although propensity score-matched risk ratio analyses demonstrated similar

cumulative incidences of mortality and cardiovascular events between tadalafil 5 mg and tadalafil 20 mg, Kaplan–Meier survival analyses demonstrated significantly improved overall survival and cardiovascular disease-free survival among patients receiving tadalafil 20 mg. To our knowledge, few previous studies have directly compared long-term clinical outcomes between these two tadalafil dosing strategies in a large real-world population.

Comparison with previous studies

Our findings are consistent with accumulating evidence suggesting that PDE5 inhibitor therapy may confer cardiovascular benefits beyond the treatment of ED. Jehle and colleagues recently demonstrated that treatment with tadalafil and sildenafil was associated with substantial reductions in mortality, major adverse cardiovascular events, dementia, and renal outcomes in a large TriNetX cohort, highlighting the potential systemic benefits of chronic PDE5 inhibition [14]. Similarly, Kloner et al. reported lower risks of major adverse cardiovascular events and all-cause mortality among men with ED receiving PDE5 inhibitors compared with untreated individuals in a nationwide healthcare database [17]. Goberdhan et al. further demonstrated that tadalafil use among men with LUTS was associated with a reduced incidence of major adverse cardiovascular events and venous thromboembolism [16], while a recent systematic review and meta-analysis by Soulaïdopoulos et al. concluded that long-term PDE5 inhibitor therapy was associated with reduced cardiovascular events and mortality across multiple observational studies [15].

Our study extends these observations by evaluating two different tadalafil dosing regimens separately rather than analysing PDE5 inhibitors as a single therapeutic class. The findings indicate that both tadalafil 5 mg and tadalafil 20 mg are associated with favourable long-term outcomes compared with non-users, supporting the possibility that tadalafil may be associated with favourable cardiovascular outcomes beyond symptomatic improvement of ED and LUTS.

Potential biological mechanisms

Several biological mechanisms may explain the observed associations. PDE5 inhibition enhances nitric oxide–cyclic guanosine monophosphate signalling, resulting in vascular smooth muscle relaxation, improved endothelial function, and enhanced tissue perfusion. Beyond these haemodynamic effects, experimental studies suggest that PDE5 inhibitors reduce oxidative stress, inhibit inflammatory signalling pathways, attenuate vascular remodelling, and improve myocardial function [10,11]. Improvements in endothelial health may slow the progression of atherosclerosis and reduce the likelihood of future cardiovascular events.

Tadalafil possesses pharmacokinetic characteristics that distinguish it from other PDE5 inhibitors. Its prolonged elimination half-life of approximately 17.5 hours permits sustained PDE5 inhibition, which may contribute to persistent endothelial benefits [9]. In addition, tadalafil has established efficacy in pulmonary arterial hypertension [12], further supporting its favourable vascular effects. Collectively,

these mechanisms provide biological plausibility for the observed reductions in mortality and cardiovascular events in the present study.

Clinical implications

The coexistence of ED and LUTS is common in ageing men and is frequently accompanied by hypertension, diabetes mellitus, obesity, and other cardiovascular risk factors. Consequently, treatment decisions often extend beyond symptom control and may influence long-term health outcomes.

Our findings suggest that tadalafil therapy may provide dual clinical benefits by improving urinary and sexual symptoms while being associated with favourable cardiovascular outcomes. These observations may be particularly relevant when counselling men with ED and LUTS who also have elevated cardiovascular risk. Nevertheless, treatment decisions should continue to be individualized according to symptom severity, patient preference, contraindications, and existing clinical guidelines [8,6].

Importantly, the observed associations should not be interpreted as evidence supporting the use of tadalafil solely for cardiovascular risk reduction. Randomized controlled trials remain necessary before such recommendations can be incorporated into routine clinical practice.

Interpretation of the head-to-head comparison

An interesting finding of this study was the apparent difference between the propensity score-matched risk ratio analyses and the Kaplan–Meier survival analyses comparing tadalafil 5 mg and tadalafil 20 mg. While cumulative risk ratios suggested comparable incidences of mortality and cardiovascular events between the two dosing regimens, time-to-event analyses demonstrated significantly improved overall survival and cardiovascular disease-free survival among patients receiving tadalafil 20 mg.

These findings are not necessarily contradictory because risk ratios and hazard ratios evaluate different aspects of treatment effect. Risk ratios compare cumulative event frequencies during follow-up, whereas hazard ratios derived from Kaplan–Meier analyses account for both the occurrence and timing of events while appropriately handling censored observations. Consequently, survival analyses may detect temporal differences that are not fully reflected by cumulative incidence measures.

Several additional factors may also have contributed to the observed findings. Patients prescribed tadalafil 20 mg on demand may differ from those receiving tadalafil 5 mg once daily with respect to baseline sexual activity, functional status, healthcare-seeking behaviour, and overall health. Although propensity score matching reduced measured baseline differences, residual confounding from unmeasured variables—including smoking status, physical activity, socioeconomic status, and medication adherence—cannot be excluded. Therefore, while the survival analyses demonstrated statistically significant advantages associated with tadalafil 20 mg, these findings should be interpreted as associations rather than evidence of superior efficacy.

Possible explanations for the observed superiority of tadalafil 20 mg

The apparent survival advantage associated with tadalafil 20 mg despite the continuous PDE5 inhibition provided by daily tadalafil 5 mg warrants careful consideration. Several explanations are plausible. First, patients prescribed tadalafil 20 mg on demand may represent a healthier subgroup with better baseline functional status, preserved sexual activity, and fewer unmeasured comorbidities, introducing a potential healthy-user effect that may not be fully accounted for by propensity score matching. Second, intermittent administration of tadalafil 20 mg results in higher peak plasma concentrations than the 5 mg daily regimen, which could theoretically influence vascular responses; however, whether this pharmacokinetic difference translates into superior long-term cardiovascular protection remains unknown [9]. Third, prescribing patterns may differ between treatment groups. Daily tadalafil 5 mg is frequently prescribed for men with bothersome LUTS secondary to benign prostatic hyperplasia, whereas tadalafil 20 mg is more commonly prescribed for men seeking treatment primarily for ED. Differences in the efficacy and use of daily versus on-demand tadalafil regimens have been described in previous clinical literature [19,20]. Finally, differences in medication adherence and persistence may also contribute. Patients who request on-demand therapy may remain more engaged in sexual activity and healthcare, potentially reflecting better overall health and lifestyle behaviours that are not captured within the database. Consequently, the observed association favouring tadalafil 20 mg should be interpreted cautiously and should not be considered evidence of superior pharmacological efficacy. Prospective randomized controlled trials are required to determine whether these findings reflect a true treatment effect or residual confounding.

Strengths and limitations

The principal strengths of this study include the large multicentre real-world cohort derived from the TriNetX Research Network, inclusion of more than one million eligible patients, and the use of propensity score matching to reduce confounding. In addition, this study is among the first to directly compare long-term clinical outcomes between daily tadalafil 5 mg and on-demand tadalafil 20 mg in routine clinical practice.

Several limitations should be acknowledged. First, the retrospective observational design precludes causal inference. Second, residual confounding from unmeasured variables may persist despite propensity score matching. Third, medication prescriptions do not necessarily reflect actual treatment adherence or persistence. Fourth, important lifestyle variables, including smoking, alcohol consumption, physical activity, body mass index, and socioeconomic status, were unavailable within the database. Fifth, disease severity, erectile function scores, LUTS severity, laboratory findings, and blood pressure measurements were not consistently available. Finally, selection bias may exist because patients prescribed tadalafil 20 mg may represent a healthier population capable of engaging in sexual activity, whereas tadalafil 5 mg is more commonly prescribed for men with bothersome LUTS secondary to benign prostatic hyperplasia. These limitations should be considered when interpreting the observed associations.

CONCLUSION

In this large real-world retrospective cohort study, both tadalafil 5 mg once daily and tadalafil 20 mg on demand were associated with significantly lower risks of all-cause mortality and individual cardiovascular outcomes compared with non-use of phosphodiesterase type 5 (PDE5) inhibitors among men aged ≥ 40 years with erectile dysfunction and/or lower urinary tract symptoms. These findings are consistent with growing evidence suggesting that tadalafil may be associated with favourable systemic cardiovascular outcomes beyond its established role in the management of erectile dysfunction and lower urinary tract symptoms.

In direct propensity score-matched comparisons, tadalafil 20 mg was associated with improved overall survival and cardiovascular disease-free survival compared with tadalafil 5 mg in time-to-event analyses. However, because this was a retrospective observational study, these findings should be interpreted as associations rather than evidence of a causal treatment effect. Residual confounding, differences in prescribing practices, and unmeasured patient characteristics may have influenced the observed outcomes.

Overall, our findings suggest that tadalafil therapy may offer favourable long-term cardiovascular outcomes in addition to symptomatic improvement in men with erectile dysfunction and/or lower urinary tract symptoms. Prospective randomized controlled trials are warranted to confirm these observations and to determine whether different tadalafil dosing strategies have distinct effects on long-term cardiovascular outcomes.

Abbreviations

AMI

Acute myocardial infarction

BMI

Body mass index

BPH

Benign prostatic hyperplasia

CI

Confidence interval

cGMP

Cyclic guanosine monophosphate

CKD

Chronic kidney disease

CVD

Cardiovascular disease

ED

Erectile dysfunction

EHR

Electronic health record

GDPR
General Data Protection Regulation
HIPAA
Health Insurance Portability and Accountability Act
HR
Hazard ratio
ICD-10
International Classification of Diseases,Tenth Revision
IHD
Ischaemic heart disease
LUTS
Lower urinary tract symptoms
MACE
Major adverse cardiovascular events
NO
Nitric oxide
PDE5
Phosphodiesterase type 5
PSM
Propensity score matching
RR
Risk ratio
SMD
Standardized mean difference
TriNetX
TriNetX Research Network.

Declarations

Ethics approval and consent to participate

This study was conducted using the TriNetX Research Network database accessed through **Taichung Veterans General Hospital (VGHTC), Taiwan**. The TriNetX platform contains only retrospective, de-identified electronic health record data, and no identifiable patient information was available to the investigators. In accordance with institutional policy and the use of fully anonymized data, formal ethical approval and informed consent were not required for this study. The TriNetX platform complies with the Health Insurance Portability and Accountability Act (HIPAA) and the General Data Protection Regulation (GDPR), ensuring the protection of patient privacy.

Consent for publication

Not applicable. This study used only de-identified retrospective data obtained from the TriNetX Research Network and does not contain any individual person's identifiable information.

Availability of data and materials

The data that support the findings of this study were obtained from the **TriNetX Research Network** through the institutional subscription of **Taichung Veterans General Hospital (VGHTC), Taiwan**. The data are de-identified and subject to data use agreements with TriNetX; therefore, they are not publicly available. Researchers may obtain access to the TriNetX platform through an institutional subscription and appropriate data use agreements. Additional information regarding the TriNetX Research Network is available at <https://trinetx.com>.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yeow Siong Lee conceived and designed the study, drafted the manuscript, and contributed to the interpretation of the data. Gu-Shun Lai performed data acquisition and formal data analysis. Chuan-Shu Chen contributed to the study conception and design, supervised the research, and critically revised the manuscript for important intellectual content. Jian-Yi Li critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

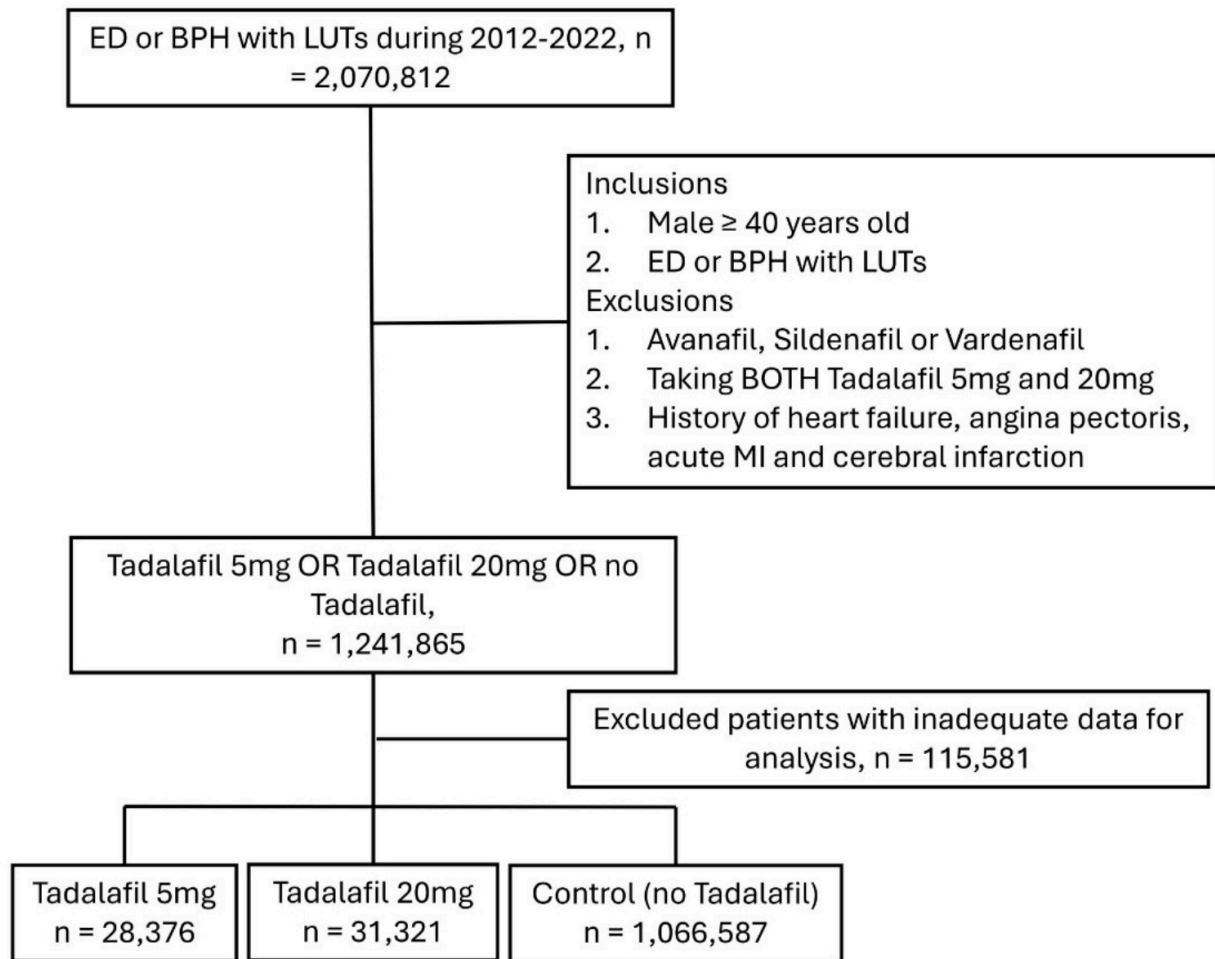


Figure 1

Flow diagram illustrating patient identification, eligibility assessment, application of exclusion criteria, and final cohort selection.

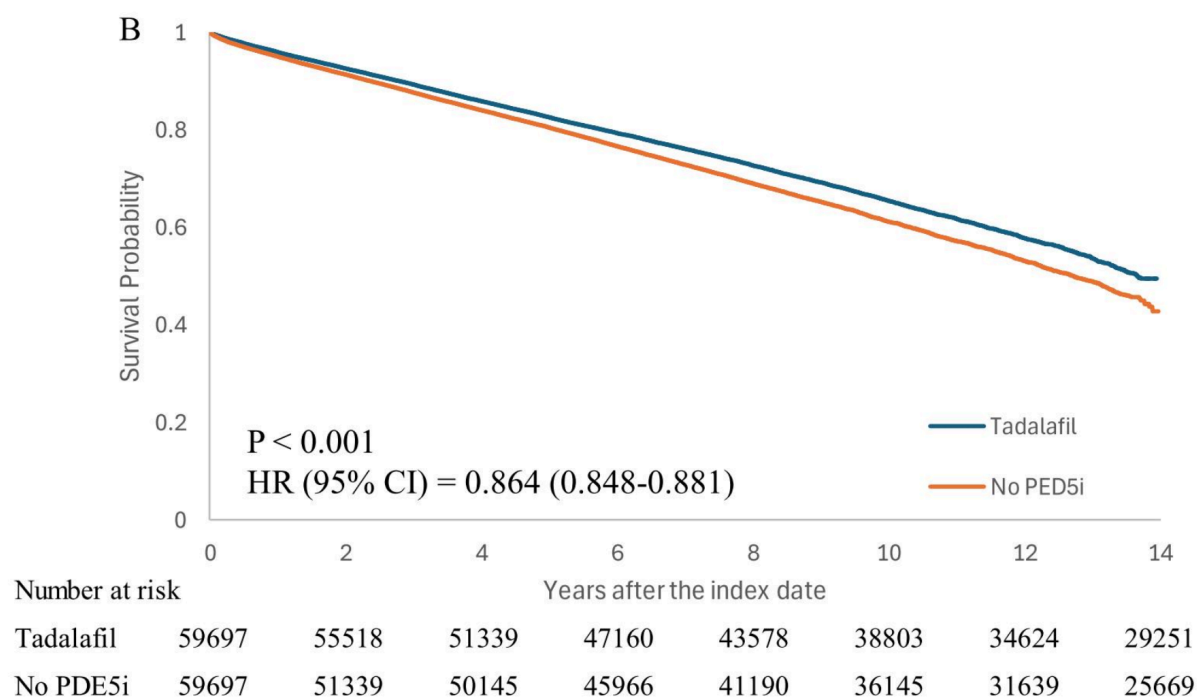
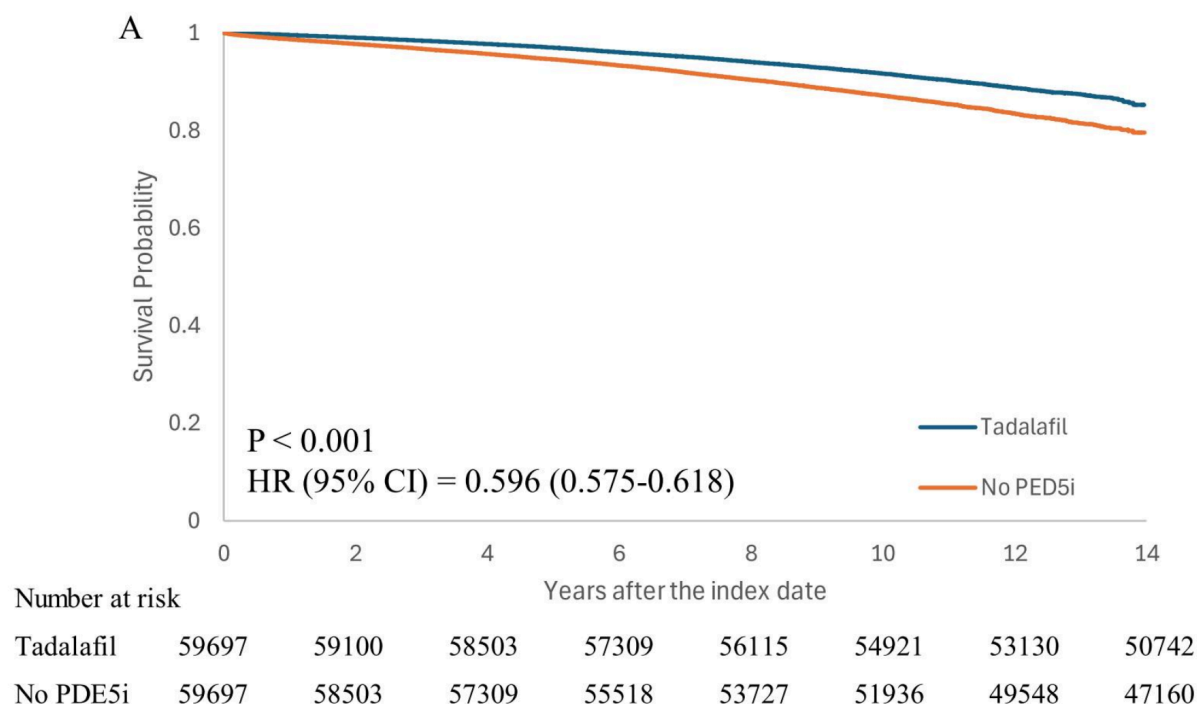


Figure 2

Kaplan–Meier survival curves comparing (A) overall survival and (B) cardiovascular disease-free survival between tadalafil users and non-users following propensity score matching.

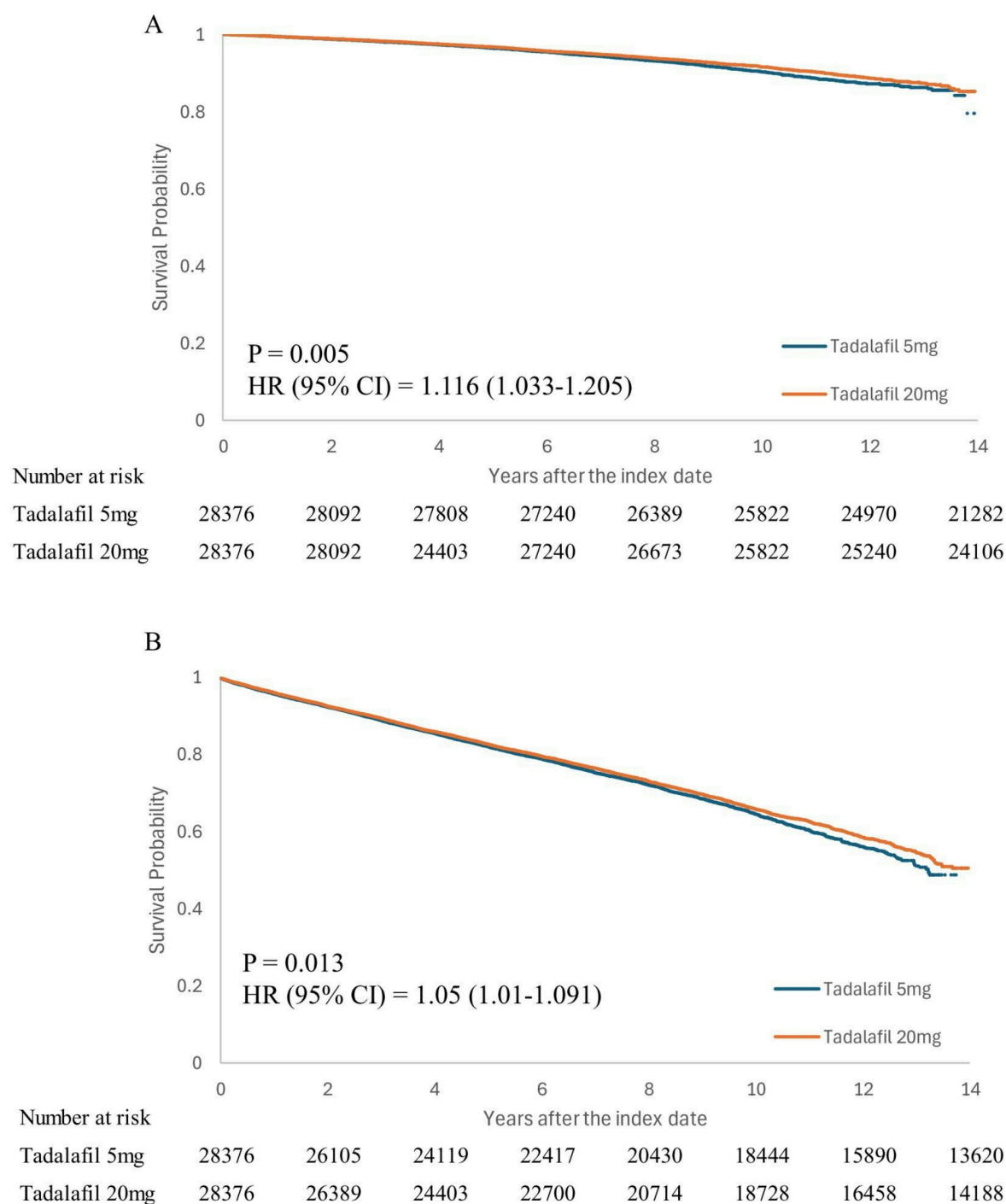


Figure 3

Kaplan–Meier survival analyses comparing tadalafil 5 mg once daily and tadalafil 20 mg on demand after propensity score matching. (A)Overall survival (HR 1.116, 95% CI 1.033–1.205; log-rank $P = 0.005$). (B)Cardiovascular disease-free survival (HR 1.050, 95% CI 1.010–1.091; log-rank $P = 0.013$). Hazard ratios are reported using the tadalafil 5 mg cohort as the reference group; therefore, HR values >1 indicate a lower hazard among patients receiving tadalafil 20 mg. Cardiovascular disease-free survival

was defined as the time from the index date to the first occurrence of acute myocardial infarction, heart failure, cerebral infarction, angina pectoris, or all-cause mortality.