CLINICAL RESEARCH STUDY

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Benefits of Tadalafil and Sildenafil on Mortality, Cardiovascular Disease, and Dementia

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ABSTRACT

BACKGROUND: Erectile dysfunction and lower urinary tract symptoms, from benign prostatic hyperplasia and bladder neck obstructions, are prevalent in men and associated with an increased risk of cardiovascular diseases. Phosphodiesterase-5 (PDE-5) inhibitors, such as tadalafil and sildenafil, are used to treat erectile dysfunction and may also offer cardiovascular benefits due to their vasodilatory effects. This study evaluates the impact of these PDE-5 inhibitors on all-cause mortality, cardiovascular disease, and dementia in middle-aged men with erectile dysfunction and lower urinary tract symptoms over a 3 year follow-up period.

METHODS: This longitudinal study analyzed data from 50 million US men using the TriNetX database. Men at least 40 years of age prescribed tadalafil or sildenafil after an erectile dysfunction diagnosis, or tadalafil after lower urinary tract symptom diagnoses, from 2004 to 2021 were included. Three-year outcomes assessed included all-cause mortality, cardiovascular disease, and dementia, comparing men on PDE-5 inhibitors to those not on these medications. Propensity matching was performed for demographics and eight pre-existing conditions.

RESULTS: The final cohort included 509,788 men with erectile dysfunction and 1,075,908 with lower urinary tract symptoms. Tadalafil and sildenafil were associated with significantly reduced risks of all-cause mortality (RR 0.66/0.76), myocardial infarction (0.73/0.83), stroke (0.66/0.78), venous thromboembolism (0.79/0.80), and dementia (0.68/0.75) in erectile dysfunction patients, with tadalafil showing more significant benefits. In lower urinary tract symptom patients, tadalafil was similarly associated with reduced mortality, cardiovascular disease, and dementia.

CONCLUSIONS: In conclusion, tadalafil and sildenafil use in erectile dysfunction patients reduced mortality, cardiovascular disease, and dementia risks, with tadalafil providing more benefits. Tadalafil also conferred similar benefits to patients with lower urinary tract symptoms.

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INTRODUCTION

Cardiovascular diseases, including myocardial infarctions, and strokes, are major causes of mortality in the United States.[1] The development of these conditions is influenced by a combination of environmental, genetic, and lifestyle factors. Erectile dysfunction and lower urinary tract symptoms have both been linked to an increased risk of cardiovascular disease.[2,3] Effective management of these conditions is crucial for reducing morbidity and mortality.[4]

Phosphodiesterase-5 (PDE-5) inhibitors, such as tadalafil and sildenafil, have emerged as potential therapeutic agents for cardiovascular disease due to their ability to inhibit the degradation of cGMP in smooth muscle, leading to relaxation and improved blood flow.[5] They are believed to offer cardiovascular benefits through vasodilation, enhanced endothelial function, and improved sexual activity.[5,6] These medications are FDA-approved for treating erectile dysfunction, idiopathic pulmonary hypertension, and lower urinary tract symptoms associated with benign prostatic hyperplasia.[6]

CLINICAL SIGNIFICANCE

- Tadalafil and sildenafil are increasingly being prescribed for erectile dysfunction and lower urinary tract symptoms.
- Tadalafil and sildenafil are associated with lower all-cause mortality, myocardial infarction, cerebral vascular accidents, venous thromboembolism, and dementia.
- Tadalafil is associated with significantly more cardiovascular benefits compared to sildenafil in erectile dysfunction patients.

Research has explored the cardiovascular benefits of PDE-5 inhibitors, with several smaller studies indicating that these medications may reduce cardiovascular complications and mortality in patients with erectile dysfunction.[7,8] However, many of these studies focused on specific populations, such as those with Type 2 diabetes.[8] Retrospective longitudinal analyses have suggested that PDE-5 inhibitors may lower the incidence of major adverse cardiovascular events (MACE), mortality, and venous thromboembolisms; however, no clear comparisons between doses were assessed.[7,9,10] Evidence from animal models and retrospective studies also hints at cognitive benefits, but large-scale clinical trials are lacking.[11,12]

This longitudinal study aims to evaluate the effects of tadalafil and sildenafil on all-cause mortality, and the development of myocardial infarction, cerebrovascular accidents (stroke), venous thromboembolism, and dementia over a 3 year follow-up period using a large, real-world database.

METHODS

Data collection and analysis for this study was performed retrospectively using the TriNetX database, a global health research network that is both HIPAA and GDPR-compliant.[13] The US Collaborative Network within the TriNetX platform was utilized, which consisted of 62 healthcare organizations (HCOs) including large academic medical institutions, specialty physicians' services, and community hospitals to provide deidentified EMR data (diagnoses, procedures, medications, and laboratory values) of over 50 million male patients within the United States.

Cohort Definition

Cohorts were developed within the TriNetX database to compare patient populations using ICD-10 codes. A primary analysis was conducted of men at least 40 years old with erectile dysfunction (ICD10: N52) without a history of cardiovascular disease (Figure 1) who were given any dose of tadalafil (RXNORM:358263) without other PDE-5 inhibitors within 6 months on or after the diagnosis compared to a similar group who were not given any PDE-5 inhibitors. The study period was between February 22, 2004 to February 22, 2021. PDE-5 inhibitors were defined as tadalafil, avanafil (RXNORM:1291301), vardenafil (RXNORM:306674), or sildenafil (RXNORM:13641). Cardiovascular disease was defined as patients with a diagnosis of acute myocardial infarction (ICD10:I21), heart failure (ICD10:I50), cerebral infarction (ICD10:I63), or unstable angina (ICD10:I20.0).

The same cohorts were compared for patients who received tadalafil 5 mg (RXNORM:358263) within 6 months on or after the diagnosis of erectile dysfunction without any other PDE-5 inhibitors. The comparison with tadalafil 5 mg was chosen as this is often utilized in chronic therapy versus as-needed treatment for the higher doses. Another analysis was performed to compare patients who received any dosage of sildenafil within 6 months on or after the diagnosis of erectile dysfunction versus the same patient population who did not receive any PDE-5 inhibitors. Patients given avanafil, vardenafil, or tadalafil were excluded from this sildenafil analysis to avoid confounding. A subgroup analysis was performed comparing any dose of tadalafil without any other PDE-5 inhibitors versus any dose of sildenafil without any other PDE-5 inhibitors.

Secondary Analysis with Lower Urinary Tract Symptoms

A secondary analysis was conducted to compare men at least 40 years old with lower urinary tract symptoms without a history of cardiovascular disease who were given any dosage of tadalafil within 6 months on or after the diagnosis compared to the same population not given any PDE-5

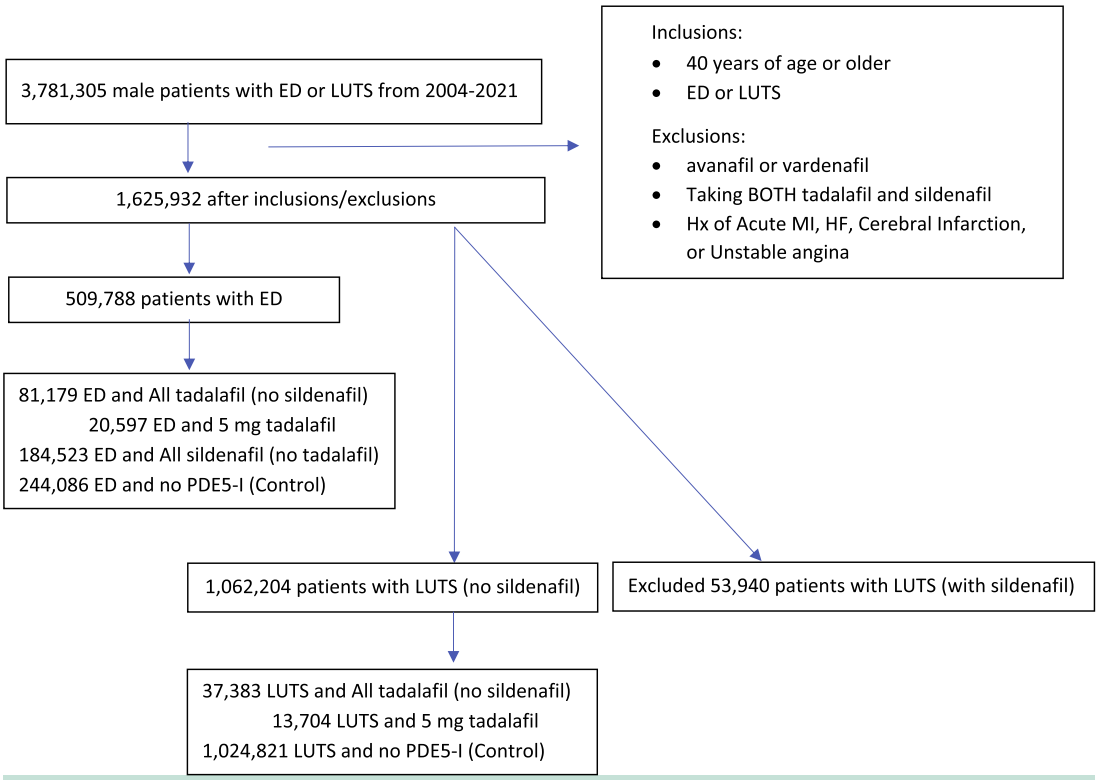

Figure 1 Study cohort flow chart.
ED = erectile dysfunction; HF = heart failure; LUTS = lower urinary tract symptoms; MI = myocardial infarction; PDE5-1 = phosphodiesterase -5 inhibitor

inhibitors. The same cohorts were again compared for patients who received tadalafil 5 mg within 6 months on or after the diagnosis of lower urinary tract symptoms without any other PDE-5 inhibitors. Lower urinary tract symptoms was defined as patients with a diagnosis of obstructive and reflux uropathy (ICD10:N13), overactive bladder (ICD10:N32.81), benign prostatic hyperplasia with lower urinary tract symptoms (ICD10:N40.1), nodular prostate with lower urinary tract symptoms (ICD10:N40.3), pain associated with micturition (ICD10:R30), vesical tenesmus (ICD10:R30.1), frequency of micturition (ICD10:R35.0), nocturia (ICD10:R35.1), other and unspecified symptoms and signs involving the genitourinary system (ICD10:R39), feeling of incomplete bladder emptying (ICD10:R39.14), or straining to void (ICD10:R39.16). Patients given avanafil, vardenafil, or sildenafil were excluded from this secondary analysis.

A posthoc analysis was done to evaluate the impact of socioeconomic status and potential confounders related to affordability and accessibility for the prescriptions of tadalafil at all dosages and outcomes in patients with erectile dysfunction or lower urinary tract symptoms. Tadalafil is fairly affordable at present, although initially, it was moderately expensive. This posthoc analysis was performed to ensure that prescriptions for tadalafil did not just represent higher socioeconomic status. The presence of the ICD-10-codes Z56.0 (Unemployment, unspecified) or Z59 (Problems related to housing and economic circumstances) was used as a marker for lower socioeconomic status and was evaluated for the tadalafil group.

Outcomes

We examined 5 outcomes in this study including all-cause mortality, myocardial infarction (ICD10:I21), stroke (ICD10:I63), venous thromboembolism (ICD10:I82), and dementia (ICD10:F02 and ICD10:F03). Cardiovascular outcomes were defined as myocardial infarction, stroke, and venous thromboembolism. The outcomes were measured from the day of the index event to 3 years after the index event.

Statistical Analysis

A 1:1 propensity score matching was done with linear regression for continuous variables and logistic regression for binary outcomes for each analysis. Patients were matched for the following pre-existing diseases: diabetes mellitus (ICD10:E08-E13), acute kidney failure and chronic kidney disease (ICD10:N17-N19), overweight and obesity (ICD10:E66), cardiac arrest (ICD10:I46), ischemic heart diseases (ICD10:I20-I25), malignant neoplasm of bronchus and lung (ICD10:C34), COPD (ICD10:J44), and hypertension (ICD10:I10-I16). Greedy nearest-neighbor matching was utilized as described in Supplementary file, Page 3. This study methodology has been previously validated.[13,14] Comparisons were made between cohorts

before and after propensity matching for both the primary (erectile dysfunction) and secondary (lower urinary tract symptoms) analysis. After propensity matching, all of the standard mean differences of the covariates were less than 0.1, indicating a well-balanced match.

Univariate analysis with chi-square and t-test was performed in TriNetX on February 22, 2024, for each cohort, reported as descriptive statistics, risk ratios (RRs), 95% confidence intervals (CIs) of these ratios, and probability values (*P*-values). Utilization of the data from TriNetX does not require UTMB IRB review as this is an analysis of deidentified data and is considered "not human subjects research."

RESULTS

A total of 3,781,305 male patients with erectile dysfunction or lower urinary tract symptoms were identified from 2004 to 2021. After exclusions, 1,625,932 patients 40 years and older with either condition were analyzed. For erectile dysfunction, 81,179 patients (15.9%) received tadalafil, 20,597 (25.4% of all dosages) of whom received tadalafil 5 mg. Additionally, 184,523 patients (36.2%) received sildenafil, and 244,086 (47.9%) received no PDE-5 inhibitors. For lower urinary tract symptoms, 37,383 patients (3.5%) received tadalafil, with 13,704 (36.7% of all dosages) receiving tadalafil 5 mg. The remaining 1,024,821 patients (96.5%) did not any receive PDE-5 inhibitors (Figure 1, Table 1).

Tadalafil Versus No PDE-5 Inhibitors in Erectile Dysfunction

Patients with erectile dysfunction who received tadalafil showed reduced all-cause mortality, improved cardiovascular outcomes, and lower rates of dementia compared to those who did not receive any PDE-5 inhibitors. These findings were consistent before and after propensity matching. Tadalafil 5 mg also demonstrated significant improvements in these outcomes (Table 2).

Sildenafil Versus No PDE-5 Inhibitors in Erectile Dysfunction

Sildenafil use in erectile dysfunction patients was associated with reductions in all-cause mortality, cardiovascular events, and dementia. These results were significant both before and after propensity matching (Table 2).

Tadalafil Versus Sildenafil in Erectile Dysfunction

Tadalafil was associated with significantly lower rates of all-cause mortality (RR 0.87), myocardial infarction (RR 0.87), and stroke (RR 0.85) compared to sildenafil. Rates of venous thromboembolism (RR 1.00, $P = .96$) and dementia (RR 0.89, $P = .13$) were similar between tadalafil and sildenafil (Table 2).

Tadalafil Versus No PDE-5 Inhibitors in Lower Urinary Tract Symptoms

Tadalafil use in lower urinary tract symptoms patients was linked to lower all-cause mortality, better cardiovascular outcomes, and reduced dementia rates compared to those who did not receive any PDE-5 inhibitors. This trend was consistent both before and after propensity matching. Tadalafil 5 mg also showed significant improvements in these outcomes (Table 2).

Posthoc Analysis of Socioeconomic Status

The posthoc analysis showed that patients prescribed tadalafil were slightly less likely to be unemployed or face housing and economic issues compared to those not prescribed PDE-5 inhibitors, showing relative risks that varied by only 1%-4%. This factor had minimal impact on the primary analysis results.

DISCUSSION

In this study, it was shown that men aged 40 years and older with erectile dysfunction prescribed tadalafil experienced significant reductions in all-cause mortality, myocardial infarction, stroke, venous thromboembolism, and dementia, compared to those not using PDE-5 inhibitors. Similarly, sildenafil also showed significant reductions in these outcomes. Tadalafil was particularly associated with better cardiovascular outcomes than sildenafil, with statistical significance confirmed both before and after propensity matching.

A secondary analysis of men aged 40 years and older with lower urinary tract symptoms but without cardiovascular disease within five years of lower urinary tract symptoms incidence revealed that tadalafil 5 mg daily resulted in significant reductions in all-cause mortality, myocardial infarction, stroke, venous thromboembolism, and dementia compared to no PDE-5 inhibitor treatment. These results align with previous reviews, which noted an independent association between tadalafil and major adverse cardiovascular events (MACE), showing benefits in all-cause mortality and reduced venous thromboembolism risk.[10]

Tadalafil's recommended dosage ranges from 5 mg to 20 mg daily, and clinical practice often involves titration to balance efficacy and side effects. A recent cohort study of 48,692 men with erectile dysfunction and high cardiovascular risk noted a dose-dependent reduction in overall mortality and MACE. This supports our findings that chronic daily tadalafil (5 mg) is at least as effective as as-needed doses.[9]

Tadalafil may be more effective than sildenafil due to its longer half-life (17.5 hours in healthy men and up to 21.6 hours in elderly men) compared to sildenafil's approximately 4 hours. This extended therapeutic window and daily dosing could explain why tadalafil is favored in this study.[15] This corresponds to a therapeutic window of tadalafil of approximately 36 hours. In addition, tadalafil is often prescribed as a daily dose both for erectile dysfunction and for lower urinary tract symptoms. The continuous

Table 1 Study Characteristics of Tadalafil All Dosages (n = 81,179) Versus No PDE5-Inhibitors (n = 244,086) in Erectile Dysfunction Patients

Demographics Cohort		Before Propensity Score Matching					After Propensity Score Matching				
		Mean ± SD	Patients	% of Cohort	*P* Value	Std Diff.	Mean ± SD	Patients	% of Cohort	*P* Value	Std Diff.
1†	Age at index	58.4 ± 9.6	81,143	100%	< .001*	0.194	58.4 ± 9.6	81,138	100%	= .66	0.002
2‡		60.3 ± 10.3	235,478	100%			58.4 ± 9.6	81,138	100%		
1	White		57,017	70.3%	< .001*	0.016		57,017	70.3%	= .09	0.008
2			163,696	69.5%				57,330	70.7%		
1	American Indian or		196	0.2%	= .81	0.001		196	0.2%	= .08	0.009
2	Alaska Native		580	0.2%				163	0.2%		
1	Unknown race		8,688	10.7%	< .001*	0.016		8,683	10.7%	= .18	0.007
2			24,091	10.2%				8,518	10.5%		
1	Native Hawaiian or		105	0.1%	< .001*	0.018		105	0.1%	= .84	0.001
2	other Pacific Islander		473	0.2%				108	0.1%		
1	Unknown ethnicity		19,810	24.4%	= .89	0.001		19,810	24.4%	= .34	0.005
2			57,547	24.4%				19,976	24.6%		
1	Not Hispanic or Latino		57,326	70.6%	< .001*	0.041		57,321	70.6%	= .49	0.003
2			161,899	68.8%				57,195	70.5%		
1	Hispanic or Latino		4,007	4.9%	< .001*	0.080		4,007	4.9%	= .65	0.002
2			16,032	6.8%				3,967	4.9%		
1	Black or African		10,880	13.4%	< .001*	0.030		10,880	13.4%	= .82	0.001
2	American		34,048	14.5%				10,911	13.4%		
1	Other race		2,748	3.4%	= .13	0.006		2,748	3.4%	= .11	0.008
2			8,244	3.5%				2,632	3.2%		
1	Asian		1,509	1.9%	= .80	0.001		1,509	1.9%	= .54	0.003
2			4,346	1.8%				1,476	1.8%		
Diagnosis											
Cohort		Mean ± SD	Patients	% of Cohort	*P* Value	Std Diff.	Mean ± SD	Patients	% of Cohort	*P* Value	Std Diff.
1	Diabetes mellitus		12,974	16.0%	= .42	0.003		12,974	16.0%	= .55	0.003
2			37,935	16.1%				13,063	16.1%		
1	Acute kidney failure and		4,086	5.0%	= .20	0.005		4,086	5.0%	= .33	0.005
2	chronic kidney disease		12,128	5.2%				4,000	4.9%		
1	Overweight and obesity		10,969	13.5%	< .001*	0.107		10,964	13.5%	= .24	0.006
2			23,723	10.1%				10,803	13.3%		
1	Cardiac arrest		33	0.0%	= .13	0.006		33	0.0%	= .10	0.008
2			129	0.1%				21	0.0%		
1	Ischemic heart diseases		5,909	7.3%	< .001*	0.022		5,909	7.3%	= .63	0.002
2			18,547	7.9%				5,858	7.2%		
1	Malignant neoplasm of		223	0.3%	< .001*	0.015		223	0.3%	= .04*	0.010
2	bronchus and lung		842	0.4%				181	0.2%		
1	Other chronic obstructive		2,160	2.7%	< .001*	0.027		2,160	2.7%	= .14	0.007
2	pulmonary disease		7,348	3.1%				2,066	2.5%		
1	Hypertensive diseases		33,326	41.1%	< .001*	0.154		33,321	41.1%	= .53	0.003
2			79,249	33.7%				33,446	41.2%		

PDE5 = Phosphodiesterase Type-5; SD = Standard Deviance; Std Diff. = Standard Difference.
†Cohort 1 = History of Erectile Dysfunction and Tadalafil All Dosages.
‡Cohort 2, History of Erectile Dysfunction and No PDE5-inhibitors.
*Statistically significant.

mechanism of action of tadalafil over time may be a reason why the data in this study favors tadalafil over sildenafil. Tadalafil may also serve as an adjunct for treatment-resistant hypertension in males with a concomitant diagnosis of erectile dysfunction. This synergistic effect with other antihypertensives can serve to benefit select patients from a mortality and vascular disease perspective,[16] as seen in this study.

Initially investigated for hypertension and angina, PDE-5 inhibitors are now known to cause erections as a side

Table 2 Mortality, Cardiovascular, and Dementia Outcomes Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
2a: Erectile dysfunction cohort						
Outcomes	**Tadalafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Tadalafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**
Deceased	1,576 (1.95%)	7,623 (3.25%)	0.60 (0.57, 0.63)	1,576 (1.95%)	2,379 (2.94%)	0.66 (0.62, 0.71)
MI	736 (0.91%)	3,101 (1.32%)	0.69 (0.64, 0.75)	736 (0.91%)	1,014 (1.25%)	0.73 (0.66, 0.80)
Stroke	655 (0.81%)	2,979 (1.27%)	0.64 (0.59, 0.69)	655 (0.81%)	993 (1.22%)	0.66 (0.60, 0.73)
VTE	1,003 (1.26%)	3,810 (1.64%)	0.77 (0.72, 0.82)	1,003 (1.26%)	1,279 (1.60%)	0.79 (0.72, 0.85)
Dementia	342 (0.42%)	1,973 (0.84%)	0.50 (0.45, 0.56)	342 (0.42%)	502 (0.62%)	0.68 (0.59, 0.78)
Outcomes	**Tadalafil 5 mg (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Tadalafil 5 mg (%)**	**No PDE5i (%)**	**RR (95% CI)**
Deceased	369 (1.80%)	7,623 (3.25%)	0.55 (0.50, 0.61)	369 (1.80%)	596 (2.90%)	0.62 (0.55, 0.70)
MI	194 (0.94%)	3,101 (1.32%)	0.72 (0.62, 0.83)	194 (0.94%)	289 (1.40%)	0.67 (0.56, 0.80)
Stroke	172 (0.84%)	2,979 (1.27%)	0.66 (0.57, 0.77)	172 (0.84%)	242 (1.18%)	0.71 (0.59, 0.86)
VTE	269 (1.33%)	3,810 (1.64%)	0.81 (0.72, 0.92)	269 (1.33%)	365 (1.80%)	0.74 (0.63, 0.86)
Dementia	93 (0.45%)	1,973 (0.84%)	0.54 (0.44, 0.66)	93 (0.45%)	134 (0.65%)	0.69 (0.53, 0.90)
Outcomes	**Sildenafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Sildenafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**
Deceased	4,334 (2.43%)	7,627 (3.25%)	0.75 (0.72, 0.77)	3,999 (2.42%)	5,241 (3.17%)	0.76 (0.73,0.80)
MI	2,072 (1.16%)	3,098 (1.32%)	0.88 (0.83, 0.93)	1,890 (1.14%)	2,274 (1.37%)	0.83 (0.78,0.88)
Stroke	1,822 (1.02%)	2,977 (1.26%)	0.80 (0.76, 0.85)	1,693 (1.02%)	2,181 (1.31%)	0.78 (0.73,0.83)
VTE	2,378 (1.35%)	3,811 (1.64%)	0.82 (0.78, 0.87)	2,188 (1.34%)	2,746 (1.68%)	0.80 (0.76,0.84)
Dementia	885 (0.50%)	1,974 (0.84%)	0.59 (0.54, 0.64)	857 (0.52%)	1,140 (0.69%)	0.75 (0.69,0.82)
Outcomes	**Tadalafil All (%)**	**Sildenafil All (%)**	**RR (95% CI)**	**Tadalafil All (%)**	**Sildenafil All (%)**	**RR (95% CI)**
Deceased	1,577 (1.95%)	4,334 (2.43%)	0.80 (0.76, 0.85)	1,577 (1.95%)	1,805 (2.23%)	0.87 (0.82, 0.93)
MI	738 (0.91%)	2,072 (1.16%)	0.79 (0.72, 0.86)	738 (0.91%)	846 (1.04%)	0.87 (0.79, 0.96)
Stroke	655 (0.81%)	1,822 (1.02%)	0.79 (0.73, 0.87)	655 (0.81%)	772 (0.95%)	0.85 (0.77, 0.94)
VTE	1,005 (1.26%)	2,378 (1.35%)	0.93 (0.87, 1.00)	1,005 (1.26%)	1,007 (1.26%)	1.00 (0.92, 1.09)
Dementia	342 (0.42%)	885 (0.50%)	0.85 (0.75, 0.97)	342 (0.42%)	383 (0.47%)	0.89 (0.77, 1.03)
2b: Lower urinary tract symptom cohort						
Outcomes	**Tadalafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Tadalafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**
Deceased	953 (2.56%)	64,512 (6.42%)	0.40 (0.37, 0.43)	953 (2.56%)	2,175 (5.84%)	0.44 (0.41, 0.47)
MI	312 (0.83%)	13,322 (1.32%)	0.63 (0.57, 0.71)	312 (0.83%)	498 (1.33%)	0.63 (0.54, 0.72)
Stroke	294 (0.79%)	12,497 (1.24%)	0.64 (0.57, 0.71)	294 (0.79%)	456 (1.22%)	0.65 (0.56, 0.75)
VTE	609 (1.66%)	23,402 (2.36%)	0.70 (0.65, 0.76)	609 (1.66%)	898 (2.45%)	0.68 (0.61, 0.75)
Dementia	231 (0.62%)	18,316 (1.83%)	0.34 (0.30, 0.39)	231 (0.62%)	511 (1.38%)	0.45 (0.39,0.53)
Outcomes	**Tadalafil 5 mg (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Tadalafil 5 mg (%)**	**No PDE5i (%)**	**RR (95% CI)**
Deceased	337 (2.47%)	64,512 (6.42%)	0.38 (0.35,0.43)	337 (2.47%)	867 (6.35%)	0.39 (0.34, 0.44)
MI	128 (0.93%)	13,322 (1.32%)	0.71 (0.59, 0.84)	128 (0.93%)	180 (1.31%)	0.71 (0.57, 0.89)
Stroke	106 (0.77%)	12,497 (1.24%)	0.62 (0.52, 0.76)	106 (0.77%)	181 (1.32%)	0.59 (0.46, 0.74)
VTE	231 (1.72%)	23,402 (2.36%)	0.73 (0.64, 0.83)	231 (1.72%)	363 (2.71%)	0.64 (0.54, 0.75)
Dementia	94 (0.69%)	18,316 (1.83%)	0.38 (0.31, 0.46)	94 (0.69%)	181 (1.33%)	0.52 (0.40, 0.66)

CI = Confidence Interval; MI = Myocardial Infarction; PDE5i = Phosphodiesterase Type-5 Inhibitor; RR = Relative Risk; VTE = Venous Thromboembolism.
*Control outcome; outcomes were within 3-years of diagnosis of ED or LUTS.

effect.[17] They have also been explored for managing angina, heart failure, stroke, and lower urinary tract symptoms. Previous studies have reported significant reductions in unstable angina, heart failure, stroke, and mortality with PDE-5 inhibitors.[7,9,10,18] Our study confirms these findings and adds that PDE-5 inhibitors also reduce all-cause mortality, myocardial infarction, stroke, and venous thromboembolism, while expanding their role in dementia.

PDE-5 inhibitors have antiaggregatory effects and increase in cGMP which may ameliorate small vessel dysfunction in the systemic and pulmonary circulation.[5,6] Outside of their cardiovascular uses mentioned above, PDE-5 inhibitors have additional uses. Literature has shown PDE-5 inhibitors to reduce hypoxic pulmonary hypertension which could aid in high-altitude illnesses.[19,20] A 2021 review article supported the nephroprotective roles of PDE-5 inhibitors in animal-based models through changes in molecular compounds affecting kidney functioning.[21] Other research has also been done studying their effects on neuropathy and fertility.[22,23]

Sildenafil and tadalafil are noteworthy in that they can cross the blood-brain barrier, as PDE-5 enzymes are expressed in brain neurons as well as subcortical white matter cells. Given this, PDE-5 inhibition may play a role in the modulation of vasodilatory responses in the CNS, decreasing the risk of dementia and Alzheimer's disease.[11] Animal models with PDE-5 inhibitors have demonstrated improvement in memory deficits after 10 weeks of treatment as well as decreased tau phosphorylation after 10 weeks of treatment; however, a change was not

demonstrated in amyloid beta levels in transgenic mice.[24] The results of this study show promise in favor of this information, demonstrating a statistically significant reduction in dementia diagnoses in the subgroup with erectile dysfunction treated with tadalafil and sildenafil versus no treatment. In addition, PDE-5 inhibitors may act to release hydrogen sulfide, the deficiency of which has been implicated in the vascular hypothesis of dementia.[25,26]

A study conducted in the United Kingdom found similar results as this study, showing an 18% lower risk of Alzheimer's dementia in men greater than or equal to 40 years of age using any PDE-5 inhibitors compared to nonusers, with sildenafil showing significant risk reduction in those over 70 with diabetes or hypertension.[27] Furthermore, individuals prescribed greater than 20 prescriptions were typically associated with a reduced risk of Alzheimer's dementia.[27] Future research should explore the effects of less commonly prescribed PDE-5 inhibitors, such as vardenafil and avanafil, on erectile dysfunction and lower urinary tract symptoms as more data become available.

STRENGTHS AND LIMITATIONS

The strengths of this study include the large cohort size, which is significantly larger than those in prior studies, the use of propensity matching to control for confounders, the utilization of data from a large, real-world database encompassing healthcare organizations across the US, and the practical implications of using relatively inexpensive medications to reduce mortality, improve cardiovascular outcomes, and lower the risk of dementia. The follow up for mortality is excellent in this database, as 94% of sites are linked to the death registries in the US. The follow up for the other outcomes could be missing if an individual sought subsequent healthcare outside of the HCOs and this is a potential limitation of this study.

This retrospective database review from multiple HCOs establishes correlations but cannot infer causality. While propensity matching accounted for diabetes mellitus, kidney failure, obesity, cardiac conditions, malignancies, COPD, and hypertension, other diseases and socioeconomic factors may not have been fully controlled. The TriNetX database has limitations in capturing comprehensive demographic factors and pre-existing conditions, which may affect the findings.

Socioeconomic factors, such as Medicaid coverage limitations on lifestyle drugs, could influence medication affordability.[28] Our posthoc analysis suggests these factors have minimal impact with only a 1%-4% difference in relative risks. The study does not address side effects like headaches, flushing, angina, or priapism, and we cannot determine if medications were discontinued due to these effects. Additionally, since both tadalafil and sildenafil are processed by the CYP450 system, interactions with other medications or dietary supplements could confound results.[29]

TriNetX, relying on EHR and insurance claim data, may have misclassification bias. The database does not track patient compliance with medications, which is crucial for chronic therapies like tadalafil. There is also uncertainty about whether tadalafil 5 mg was used as intended for chronic therapy.

The study focused on males due to FDA approval and prescription guidelines for erectile dysfunction and lower urinary tract symptoms. However, off-label use in females exists, suggesting potential cardioprotective benefits for them as well. Future research should explore outcomes such as all-cause mortality, myocardial infarction, stroke, and venous thromboembolism risk in females prescribed tadalafil.

CONCLUSION

Males 40 years of age and older with erectile dysfunction taking tadalafil experienced significant reductions in all-cause mortality, myocardial infarction, stroke, venous thromboembolism, and dementia compared to those not on the medication. Both tadalafil and sildenafil provided benefits, with tadalafil showing more favorable outcomes. In patients with lower urinary tract symptoms, tadalafil also demonstrated significant benefits. In the clinical treatment of patients, 5 mg daily dosing of tadalafil should be considered for all individuals with erectile dysfunction, or lower urinary tract symptoms. Further research is needed to explore the effects of low-dose tadalafil in patients with cardiovascular diseases and dementia risk, and randomized controlled trials should be conducted to establish causation between PDE-5 inhibitors and reductions in mortality, cardiovascular diseases, and dementia.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.amjmed.2024.10.039.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Codes Used

Diagnosis	ICD-10-CM
Male erectile dysfunction	
Male erectile dysfunction	N52
Lower urinary tract symptoms	
Obstructive and reflux uropathy	N13
Overactive bladder	N32.81
Benign prostatic hyperplasia with lower urinary tract symptoms	N40.1
Nodular prostate with lower urinary tract symptoms	N40.3
Pain associated with micturition	R30
Vesical tenesmus	R30.1
Frequency of micturition	R35.0
Nocturia	R35.1
Other and unspecified symptoms and signs involving the genitourinary system	R39
Feeling of incomplete bladder emptying	R39.14
Straining to void	R39.16
PDE-5 inhibitors	RxNorm
Avanafil	1291301
Sildenafil	136411
Vardenafil	306674
Tadalafil	358263

Supplementary Table 2 Introduction Literature Review and Comparisons

Title	Date	Cohort Size	Population	Type of Study	Outcomes Measured	Results	Weakness
Association between treatment for erectile dysfunction and death or cardiovascular outcomes after myocardial infarction	Aug 2017	88,445	All men 18-80 years of age with a first MI	Observational Epidemiological Study	All-cause mortality, Myocardial infarction, heart failure, revascularization, MACE, cardiovascular mortality, and noncardiovascular mortality	Men treated for ED had 33% reduced risk of all cause mortality compared to those w/o ED tx. Risk of hospitalization for HF was 40% lower in men with treatment for ED. There were no associations between ED tx and MI. Tx for ED decreased risk for both cardiovascular and noncardiovascular deaths. Risk of MACE during f/u was lower in men treated for ED	Only included people from Sweden. Did not stratify severity of ED. No info on dosage of ED treatments
Phosphodiesterase Type-5 inhibitor use in Type 2 diabetes is associated with a reduction in all-cause mortality	July 2016	5,956	Men aged 40-89 dx with T2DM	Retrospective	Primary: all-cause mortality	"In a population of men with Type 2 diabetes, use of PDE5is was associated with lower risk of overall mortality and mortality in those with a history of acute MI"	Grouped all PDE5i
Effect of phosphodiesterase Type-5 inhibitors on major adverse cardiovascular events and overall mortality in a large nationwide cohort of men with erectile dysfunction and cardiovascular risk factors: A retrospective, observational study based on healthcare claims and national death index data	Jan 2023	72,498	1. Men with dx ED w/o prior MACE within 1 year 2. >1 clam for PDE5i vs no claims for PDE5i 3. General population	Retrospective	Primary: MACE Secondary: Mortality Individual components of MACE	MACE lower by 13% on PDE5is Mortality and components lower Similar results for men w/o CAD	Limited to men with ED Grouped all PDE5i

Supplementary Table 2 (*Continued*)

Title	Date	Cohort Size	Population	Type of Study	Outcomes Measured	Results	Weakness
Is tadalafil associated with decreased risk of major adverse cardiac events or venous thromboembolism in men with lower urinary tract symptoms?	Apr 2022	826,596	Men w/ history of LUTS 1. No hx of Tadalafil or a-blocker 2. Hx of Tadalafil, no a-blocker 3. Hx of a-blocker, no Tadalafil 4. Hx of both Tadalafil and a-blocker	Retrospective	MACE Venous thromboembolism	**Tadalafil use was independently associated with decreased risk of MACE or VTE** (OR = 0.57, 95% CI = 0.5-0.66, $P <$ .001)	Limited to men with LUTS
PDE5 inhibitor drugs for use in dementia	Sept 2023	N/A	Humans, rodents, nonhuman primates	Literature Review	Cognitive performance and dementia risk	Mechanistic studies in rodents and nonhuman primates suggest improvements in cognitive performance and benefits in AD	Applies to animal models and not necessarily humans
Phosphodiesterase 5 inhibitor mirodenafil ameliorates Alzheimer-like pathology and symptoms by multimodal actions	July 2022	18	Wild-type and transgenic mice	Preclinical Prospective Interventional Study	Mirodenafil-induced alterations associated with cGMP, PKG, CREB pathway, apoptotic cell death, tau phosphorylation, amyloid genesis, autophagy-lysosomy pathway, GR transcriptional activity, and Wnt/B-catenin signaling	Here, mirodenafil is demonstrated to improve cognitive behavior in the APP-C105 mouse model. Mirodenafil reduced the Aβ and phosphorylated tau burdens in vivo, and also ameliorated AD pathology induced by Aβ through the modulation of cGMP/PKG/CREB signaling pathway, (GSK-3β) activity, GR transcriptional activity, and the Wnt/β-catenin signaling in neuronal cells	Applies to animal models and not necessarily humans

ED = Erectile Dysfunction; LUTS = Lower Urinary Tract Symptoms; MACE = Major Adverse Cardiac Event; MI = Myocardial Infarction; PDE5i = Phosphodiesterase Type-5 Inhibitors.

Greedy Nearest Neighbor Matching (NNM)

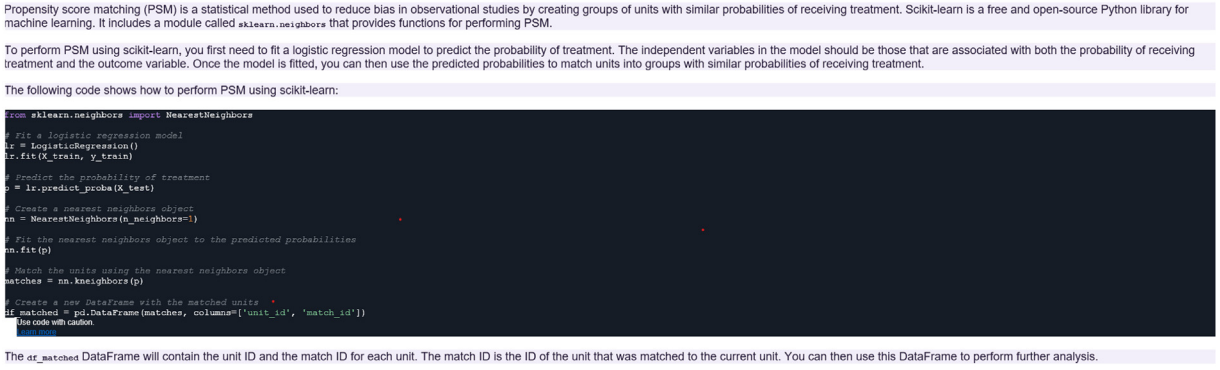
The most common implementation of propensity matching is pair-matching, in which pairs of treated and control participants are formed. There are several common implementations of pair-matching. The most commonly used is greedy nearest neighbor matching (NNM), which we used, in which a treated participant is selected at random and then matched to the control participant whose propensity score is closest to that of the treated participant. The process is described as greedy because at each stage the control is selected who is closest to the currently considered treated participant, even if that untreated participant would serve better as a control for a subsequent treated participant. This process is then repeated until a matched control participant has been selected for each treated participant. This process generally uses matching without replacement, so that once a control participant is matched to a treated participant, that control participant is no longer available for matching to a subsequent treated participant. A refinement to NNM is NNM with a caliper restriction. Using this approach, a control participant is an acceptable match for a treated participant only if the difference in their propensity scores is less than a maximum amount (the caliper width or distance). For technical reasons, one typically matches on the logit of the propensity score and uses a caliper width that is defined as a proportion of the (0.1-0.2) SD of the logit of the propensity score. A crucial step in any study that uses propensity score matching is to assess the degree to which matching on the propensity score resulted in the formation of a matched sample in which the distribution of baseline characteristics is similar between treated and control participants. This assessment is critical as it allows both the researcher and readers to assess whether matching on the estimated propensity score has removed systematic baseline differences between treatment. The use of the standardized difference, which is the difference in means in units of SD, is often used for assessing the similarity of matched treated and control participants. Some authors have suggested that

a threshold of 0.10 (or 10%) be used to denote acceptable balance after matching.[13] Once acceptable balance has been achieved, analysts can unblind themselves to the outcome and compare outcomes between treated and control participants in the matched sample. The analyses conducted in the propensity score−matched sample can be similar to those that would be done in an RCT with a similar outcome.

TriNetX Information

Topaloglu U, Palchuk MB. Using a federated network of real-world data to optimize clinical trials operations. *JCO Clin Cancer Inform*. 2018;2:1-10. doi:10.1200/CCI.17.00067.

Propensity-Score Matching Using Sci-Kit Learn


Propensity score matching (PSM) is a statistical method used to reduce bias in observational studies by creating groups of units with similar probabilities of receiving treatment. Scikit-learn is a free and open-source Python library for machine learning. It includes a module called `sklearn.neighbors` that provides functions for performing PSM.

To perform PSM using scikit-learn, you first need to fit a logistic regression model to predict the probability of treatment. The independent variables in the model should be those that are associated with both the probability of receiving treatment and the outcome variable. Once the model is fitted, you can then use the predicted probabilities to match units into groups with similar probabilities of receiving treatment.

The following code shows how to perform PSM using scikit-learn:

```
from sklearn.neighbors import NearestNeighbors

# Fit a logistic regression model
lr = LogisticRegression()
lr.fit(X_train, y_train)

# Predict the probability of treatment
p = lr.predict_proba(X_test)

# Create a nearest neighbors object
nn = NearestNeighbors(n_neighbors=1)

# Fit the nearest neighbors object to the predicted probabilities
nn.fit(p)

# Match the units using the nearest neighbors object
matches = nn.kneighbors(p)

# Create a new DataFrame with the matched units
df_matched = pd.DataFrame(matches, columns=['unit_id', 'match_id'])
```

Use code with caution.
Learn more

The `df_matched` DataFrame will contain the unit ID and the match ID for each unit. The match ID is the ID of the unit that was matched to the current unit. You can then use this DataFrame to perform further analysis.