



# Safety of Testosterone Therapy in Chronic Kidney Disease: A Propensity Score-Matched Cohort Study

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**Purpose:** Testosterone deficiency is highly prevalent in men with chronic kidney disease (CKD) and contributes to frailty, fatigue, and cognitive decline. While testosterone replacement therapy (TRT) may alleviate these complications, concerns persist regarding its cardiovascular and oncologic safety in CKD. Evidence specific to this population is lacking.

**Materials and Methods:** We performed a retrospective, propensity score-matched cohort study using the TriNetX Global Collaborative Network. Male patients aged 18–80 years with CKD stages 3–5 and hypogonadism were included. Patients were stratified by TRT exposure within six months of diagnosis. Exclusions were prior transplantation, eGFR <10 mL/min/1.73 m<sup>2</sup>, dialysis or dementia occurring within one month of CKD. Outcomes over five years included all-cause mortality (primary outcome), vascular dementia, Alzheimer's disease, stroke, myocardial infarction, heart failure, and prostate cancer. Propensity score matching (1:1) balanced demographics, comorbidities, and laboratory measures. Cox proportional hazards models estimated hazard ratios (HRs).

**Results:** After matching, 1,545 patients were included in each of the two cohorts (TRT treated or non-treated) with well-balanced characteristics (mean eGFR 47.7±15.1 mL/min/1.73 m<sup>2</sup>). Median follow-up was 3.7 years. All-cause mortality was lower in the TRT group (HR 0.78, 95% confidence interval 0.63–0.98). No significant differences were observed for cardiovascular outcomes, prostate cancer or dementia.

**Conclusions:** In men with CKD and hypogonadism, TRT was associated with improved survival and no excess risk of cardiovascular events, prostate malignancy or dementia. These findings suggest TRT is a safe therapeutic option in this high-risk population, warranting further prospective evaluation.

**Keywords:** Dementia; Health status; Hypogonadism; Renal insufficiency, chronic; Testosterone

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## INTRODUCTION

Chronic kidney disease (CKD) is a progressive con-

dition associated with significant cardiovascular and systemic complications, including cognitive impairment and an increased risk of dementia [1-3]. Several

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mechanisms contribute to the elevated risk of dementia in CKD, such as chronic inflammation, oxidative stress, vascular injury, and hormonal dysregulation [4]. Among these, testosterone deficiency is a common condition in patients with CKD [5]. Hypogonadism in men can present a variety of symptoms that affect sexual health, cognitive abilities, and physical appearance. Cognitive effects, including memory problems, difficulty concentrating are commonly present in hypogonadism. Fatigue is another common symptom, often described as exhaustion, excessive tiredness, and poor exercise performance [6]. Depression, mood swings, and sadness frequently occur and can significantly diminish quality of life (QoL). Physically, low testosterone leads to sarcopenia, less body hair, obesity, and vasomotor symptoms like hot flushes. Many of these issues are already evident in CKD patients, and hypogonadism can worsen this burden, but hypogonadism is infrequently tested in CKD patients [7]. Furthermore, testosterone deficiency has been linked to a greater risk of Alzheimer's disease (AD) and vascular dementia (VaD) in the general male population, suggesting a possible relationship between hormonal imbalance and neurodegeneration [8].

From a biological perspective, testosterone is categorized as a neurosteroid because of its ability to cross the blood-brain barrier and interact directly with neurons. Within neurons, testosterone binds to androgen receptors, which function as nuclear transcription factors. Once activated, these receptors move to the cell nucleus, where they affect the transcription of specific genes related to neuronal growth, survival, and synaptic plasticity. Testosterone enhances synaptic plasticity by modulating neurotransmitter systems, particularly the glutamatergic and GABAergic systems [9]. It is associated with promoting neurogenesis in the hippocampus, a vital brain region for learning and memory. Animal studies indicate that testosterone can increase dendritic spine density, resulting in stronger synaptic connections [10]. Testosterone possesses neuroprotective qualities, influencing the function of microglia, the brain's immune cells, which helps to reduce the release of pro-inflammatory cytokines. This neuroprotective effect is important in neurodegenerative diseases such as AD and Parkinson's, where inflammation and the loss of neurons are key characteristics [11]. The hippocampus, crucial for forming memories and navigating space, contains dense concentration of androgen

receptors. Studies show that testosterone contributes to increased hippocampal volume and boosts performance on spatial memory tasks. In older adults, testosterone replacement therapy (TRT) has been associated with enhancements in both verbal memory and visual-spatial abilities [12]. The prefrontal cortex, which regulates executive functions such as decision-making, impulse control, and working memory, is sensitive to testosterone levels. Testosterone may decrease  $\beta$ -amyloid buildup, a key feature of AD, indicating a possible protective role against cognitive decline [13]. Low testosterone is linked to higher incidence of depression, anxiety, fatigue, and low libido. It affects neurotransmitter systems, particularly diminishing dopamine and serotonin activity, which are crucial for mood regulation. TRT in hypogonadal men has been shown to improve mood, energy levels, and overall QoL [14].

Given the overlap between the mechanisms of cognitive impairment in CKD and those associated with testosterone deficiency, it is plausible that TRT could reduce dementia risk in this population, but results are inconclusive [15].

While the potential cognitive benefits of TRT have been explored in other populations, such as ageing men, the effects on dementia risk and the safety in patients with CKD remain unclear [16]. CKD represents a unique environment of systemic inflammation and metabolic dysregulation, which could alter the risk-benefit profile of TRT. Additionally, concerns about the cardiovascular safety of TRT in CKD patients warrant careful evaluation, as cardiovascular disease is a leading cause of mortality in this population [17]. However, testosterone deficiency itself has been linked to an increase in major adverse cardiac events, with one systematic review and meta-analysis (covering 5,331 patients with CKD) finding that each 1-standard deviation (SD) decrease in total testosterone independently increased the risk of all-cause mortality by 27% (hazard ratio [HR] 1.27, 95% confidence interval [CI] 1.16 to 1.38), cardiovascular mortality by 100% (HR 2.00, 95% CI 1.39 to 2.86), cardiovascular events by 20% (HR 1.20, 95% CI 1.04 to 1.39), and infectious events by 41% (HR 1.41, 95% CI 1.08 to 1.84). One possible contributor to increased cardiovascular risk in hypogonadal patients is impaired high-density lipoprotein (HDL) function [18].

The effects of TRT upon cardiovascular disease risk in the general population were the subject of several studies, which have yielded conflicting results [19].

Studies such as that by Finkle et al [20] suggested increased risk, although the study design has been questioned, whereas those by, Muraleedharan and Jones [21] have shown an improvement in cardiovascular disease amongst treated patients.

This is an epidemiological study, designed according to the PICO framework [22], aimed at verifying whether patients with CKD stages 3 to 5 who have a diagnosis of hypogonadism and treated with TRT exhibit different risks of VaD, AD, mortality, cardiovascular events, and prostate cancer compared to patients with CKD stages 3 to 5 with hypogonadism who were not receiving TRT.

## MATERIALS AND METHODS

### 1. Study design and setting

We conducted a retrospective observational cohort study on patients who had stages 3 to 5 CKD according to the KDIGO classification [23]. Data for this study were accessed and analyzed through the TriNetX LIVE using the Global Collaborative Network [24]. TriNetX is a global research network that aggregates anonymized electronic medical records (EMRs) from over 150 healthcare organizations (HCOs) around the world. These organizations consist of academic medical centers, specialty hospitals, physician groups, and community hospitals, collectively referred to as HCOs. The data includes both insured and uninsured patients, representing a variety of geographic regions, age groups, and socioeconomic backgrounds. TriNetX consistently gathers information directly from EMR systems [25]. All processes related to data collection, processing, and transmission comply with the applicable data protection laws relevant to the contributing HCOs. This includes full compliance with the EU Data Protection Law Regulation 2016/679, the General Data Protection Regulation (GDPR), and the U.S. Health Insurance Portability and Accountability Act (HIPAA). Diagnoses are coded according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), while procedures are identified using the ICD-10-PCS system, the Current Procedural Terminology (CPT), the Systematized Nomenclature of Medicine, and/or the Healthcare Common Procedure Coding System. Laboratory results are identified through the Logical Observation Identifiers Names and Codes. The need for informed consent was waived because the

data was completely anonymized.

### 2. Patient populations

We studied male patients aged 18 to 80 years with CKD stages 3 to 5 who experienced hypogonadism at any point after their CKD diagnosis, including those on dialysis, whose hypogonadism diagnosis occurred before or up to 6 months after starting dialysis. Patients' CKD stages were classified according to KDIGO criteria.

Patients were excluded if:

- Their most recent estimated glomerular filtration rate-epidemiology collaboration (eGFR-EPI) was below 10 mL/min/1.73 m<sup>2</sup>, and they were not on dialysis, to avoid including those on conservative CKD care.
- They had undergone any organ transplantation.
- They had hypogonadism but had been on dialysis for more than 6 months (only those whose first dialysis session occurred within the previous 6 months were eligible) to avoid confounders due to the dialysis treatment.
- They experienced their first dementia episode before, or within 1 month after, their CKD diagnosis.

Dementia was categorized as mild cognitive impairment (G31.84), VaD (F01), dementia attributed to other conditions (F02), unspecified dementia (F03), or AD (G30), with the respective ICD-10 codes noted in brackets.

Cohort 1 (TRT group) consisted of patients diagnosed with hypogonadism (E29 or E89.5) following their CKD diagnosis, who had initiated TRT within six months after the hypogonadism diagnosis. Patients diagnosed with dysplasia of the prostate (N42.3), carcinoma in situ of the prostate (D07.5), or malignant neoplasm of the prostate (C61) prior to their initial TRT were excluded. The TRT group included patients with one of the following diagnoses: hormone replacement therapy (Z79.890), testosterone injection (J1071, J3130, J3140, J3121, J1070, J3145, J1080, J3120, or J1060), subcutaneous hormone pellet implantation (CPT 11980 or S0189), or androgen treatment (ATC: G03B).

Cohort 2 (non-TRT group) consisted of CKD patients diagnosed with hypogonadism as per cohort 1, who had never undergone TRT treatment.

The index date for each patient in the cohort, marking their entry into the analysis, was defined as the day they first received TRT for cohort 1 (maximum six months after the diagnosis of hypogonadism) and the first day they were diagnosed with hypogonadism for

cohort 2. The report was generated using the TriNetX platform (<https://live.trinetx.com/>) on 8 May 2025. We considered events within the last 20 years, excluding any diagnoses that occurred more than 20 years prior. No patients were excluded from either cohort on these grounds, as none experienced their index event more than 20 years ago.

### 3. Pre-specified outcomes

The outcomes of interest were mortality, VaD, AD, stroke, myocardial infarction, and prostate cancer. Outcome measures were recorded within a five-year window following the diagnosis of hypogonadism. Primary outcome measures included (in brackets) the ICD-10-CM or the National Library of Medicine – Veterans Affairs vocabulary:

- Deceased or ill-defined and unknown cause of mortality (R99).
- VaD: vascular dementia (F01), dementia in other diseases classified elsewhere (F02), unspecified dementia (F03), or mild cognitive impairment (G31.84).
- AD (G30).
- Stroke: cerebral infarction (I63) or cerebrovascular diseases (I60 to I69).
- Myocardial dysfunction: heart failure (I50), acute myocardial infarction (I21), or ischemic cardiomyopathy (I25.5).
- Prostate cancer: dysplasia of the prostate (N42.3),

**Table 1.** ICD-10 code definitions and outcomes

Code	Definition
Deceased/ill-defined mortality	Death
F03	Unspecified dementia
F02	Dementia in other diseases classified elsewhere
F01	Vascular dementia
G31.84	Mild cognitive impairment of uncertain or unknown etiology
G30	Alzheimer's disease
I63	Cerebral infarction
I60–I69	Cerebrovascular diseases
I21	Acute myocardial infarction
I25.5	Ischemic cardiomyopathy
N42.3	Dysplasia of prostate
D07.5	Carcinoma in situ of prostate
C61	Malignant neoplasm of prostate
I50	Heart failure

ICD-10: International Classification of Diseases, Tenth Revision.

carcinoma in situ of the prostate (D07.5), or malignant neoplasm of the prostate (C61).

Table 1 provides a list of codes used for outcome definition.

### 4. Covariates and propensity score matching

To mitigate the impact of confounders, we applied a propensity score matching (PSM). We utilized the TriNetX built-in algorithm for PSM based on 1:1 nearest-neighbor matching with a margin of 0.1 SD. For matching, we included the age at the index event, ethnicity, comorbidities (diabetes, hypertension, neoplasms, previous history of ischemic heart diseases, cerebrovascular diseases, heart failure, or acute myocardial infarction), and nicotine dependence. Patients were also balanced for glomerular filtration rate/1.73 sq m (CKD-EPI), serum albumin (mass/volume), serum cholesterol (mass/volume), and hemoglobin A1c in blood (Table 2). We used the standardized difference (Std diff) to assess the balance of baseline characteristics in the populations matched by propensity scores. A Std diff < 0.1 indicates

**Table 2.** Variables used for propensity score matching

Code	Definition
–	Age at index date
2106-3	White
2186-5	Not Hispanic or Latino
2054-5	Black or African American
2028-9	Asian
2135-2	Hispanic or Latino
2131-1	Other race
2076-8	Native Hawaiian or other Pacific Islander
1002-5	American Indian or Alaska Native
62238-1	eGFR (CKD-EPI): Glomerular filtration rate per 1.73 m <sup>2</sup> (mL/min/1.73 m <sup>2</sup> )
TNX Curated 9045	Serum albumin (g/dL)
TNX Curated 9000	Total cholesterol (mg/dL)
TNX Curated 9037	Hemoglobin A1c (%)
ICD-10-CM I10	Essential (primary) hypertension
ICD-10-CM E08–E13	Diabetes mellitus (all types)
ICD-10-CM I20–I25	Ischemic heart diseases
ICD-10-CM C00–D49	Neoplasms (any cancer)
ICD-10-CM I50	Heart failure
ICD-10-CM I60–I69	Cerebrovascular diseases
ICD-10-CM F17	Nicotine dependence
ICD-10-CM I21	Acute myocardial infarction
ICD-10-CM I25.5	Ischemic cardiomyopathy

eGFR: estimated glomerular filtration rate, CKD: chronic kidney disease, EPI: epidemiology collaboration.

a small difference in the two cohorts.

## 5. Statistical analysis

Data processing was performed using Trinetcx's built-in algorithms. Numerical baseline characteristics are shown as mean and SD, while categorical characteristics are expressed as the number of patients with the corresponding percentage of the cohort. A t-test was employed to calculate p-values for continuous variables, with Fisher's exact test used for categorical variables. Outcomes five years after the index event (CKD diagnosis) were evaluated using the platform's compare outcomes analytic, Measures of Association, and Survival tools. The analysis includes risks and HRs with 95% CIs. Patients with outcomes occurring before the specified time frame were excluded. The Kaplan–Meier analysis estimated outcome probabilities at daily intervals. Patients were censored from the analysis after their last recorded entry. The Log-Rank test, HR, and tests for proportionality assumptions were conducted. Statistical significance was defined as a p-value < 0.05.

To explore whether CKD severity modified the association between TRT and outcomes, stratified analyses in three pre-specified subgroups was undertaken: (1) CKD stage 3a (eGFR 45 to 59 mL/min/1.73 m<sup>2</sup>); (2) more advanced non-dialysis CKD (stages 3b to 5, eGFR 10 to 44 mL/min/1.73 m<sup>2</sup>); and (3) dialysis-dependent CKD. Kidney transplant recipients were excluded a priori. The risks, HRs, and Kaplan–Meier curves were then estimated within each stratum and tested for interaction between TRT and CKD severity for mortality.

## 6. Details of the software used to run the analyses

The TriNetX platform is a customized solution designed for use in the clinical research field. The underlying technology is proprietary (TriNetX, LLC) and is protected by trade secrets. The statistical methods and software packages used to generate statistical analyses include the following: Java 11.0.16 (featuring Apache Commons Math 3.6.1), R 4.0.2 (with Hmisc1-1 and Survival 3.2-3), and Python 3.7 (incorporating lifelines 0.22.4, matplotlib 3.5.1, numpy 1.21.5, pandas 1.3.5, scipy 1.7.3, and statsmodels 0.13.2).

## 7. Ethics statement

This is a non-interventional, retrospective study utilising data obtained from TriNetX, LLC ("TriNetX")

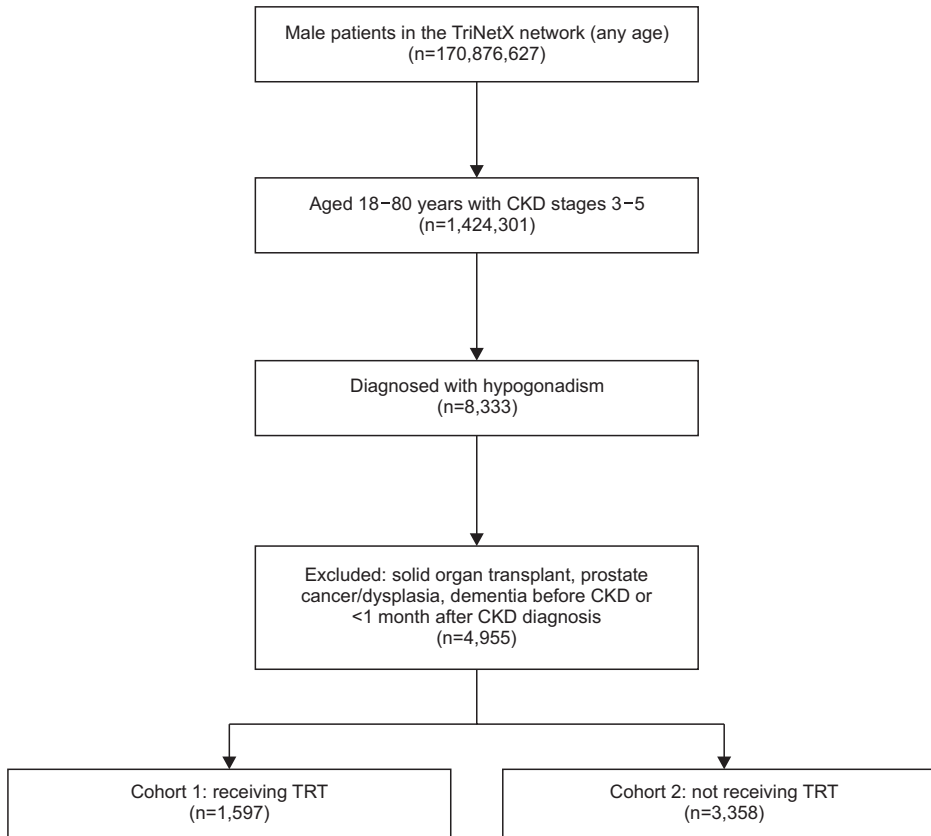
and conducted in accordance with ethical guidelines aligned with the Declaration of Helsinki, the International Conference on Harmonization, and Good Clinical Practice. TriNetX is a global federated health research network providing access to EMRs from HCOs worldwide. Research studies utilising TriNetX do not require ethical approval as part of a federated network. Participating HCOs' identities to each dataset are kept confidential, adhering to ethical norms and regulatory frameworks that prevent data re-identification. The TriNetX platform uses only aggregated counts and statistical summaries of deidentified information. No Protected Health Information or personal data is accessible to platform users. All data collection, processing, and transmission comply with applicable Data Protection laws for the contributing HCOs, including the EU Data Protection Law Regulation 2016/679, the GDPR regarding the protection of individuals in relation to personal data processing, and the HIPAA, the US federal law protecting the privacy and security of healthcare data. Individual personal data does not leave the HCO. TriNetX is ISO/IEC 27001: 2022 certified and maintains a robust IT security program to protect personal and healthcare data.

## RESULTS

We identified two cohorts of male patients aged 18 to 80 years with CKD stages 3 to 5, defined by ICD-10 diagnosis codes or the most recent eGFR-EPI between 10 to 59.9 mL/min/1.73 m<sup>2</sup>. All patients had a diagnosis of hypogonadism, defined by ICD-10 codes for testicular dysfunction (E29) or postprocedural testicular hypofunction (E89.5). Patients were excluded if they had a history of solid organ transplantation, prostate cancer, prostatic dysplasia, carcinoma in situ of the prostate, or dementia diagnosed before or within one month following CKD diagnosis. To minimize reverse causation, patients were further excluded if hypogonadism was first diagnosed more than six months after initiation of dialysis. The final study population was stratified based on TRT exposure (Fig. 1).

Cohort 1 included patients who initiated TRT on or after CKD diagnosis, with hypogonadism diagnosed within six months prior to TRT initiation (n=1,597).

Cohort 2 included patients with no evidence of TRT exposure at any time, and whose hypogonadism was diagnosed after CKD diagnosis (n=3,358).



**Fig. 1.** Individuals at each stage of the study design. CKD: chronic kidney disease, TRT: testosterone replacement therapy.

**Table 3.** Baseline demographics and comorbidities of the two cohorts before and after PSM

Characteristic	Before matching: TRT (n=1,555)	Before matching: non-TRT (n=3,216)	SMD	After matching: TRT (n=1,545)	After matching: non-TRT (n=1,545)	SMD
Age at index	64.7±9.45	67.0±9.52	0.24 <sup>a</sup>	64.8±9.34	65.1±9.85	0.02
White	81.99	79.45	0.06	82.07	83.17	0.02
Black or African American	10.74	13.40	0.08	10.74	9.84	0.02
Asian	3.92	2.71	0.06	3.82	3.56	0.01
Hispanic or Latino	3.47	4.45	0.05	3.50	3.56	0.01
eGFR	47.9±15.3	45.7±14.2	0.15 <sup>a</sup>	47.7±15.1	47.1±15.1	0.04
Hypertension	43.34	48.38	0.10	43.43	40.97	0.04
Diabetes mellitus	32.03	41.20	0.19 <sup>a</sup>	32.10	31.07	0.02
Ischemic heart disease	12.48	19.06	0.18 <sup>a</sup>	12.56	11.20	0.04
Heart failure	5.92	11.54	0.20 <sup>a</sup>	5.96	4.73	0.05

Values are presented as mean±standard deviation or percentage only.

PSM: propensity score matching, TRT: testosterone replacement therapy, SMD: standardized mean differences, eGFR: estimated glomerular filtration rate.

<sup>a</sup>SMD greater than 0.1, indicating cohort imbalance.

After 1:1 PSM, each cohort had 1,545 patients with well-balanced baseline characteristics (all standardized mean differences <0.1), including age, race/ethnicity, eGFR, and comorbidities such as hypertension, diabetes, and cardiovascular disease, and receiving dialysis (1.2% and 1.6% in the TRT group and 1.6% in the un-

treated group) (Table 3).

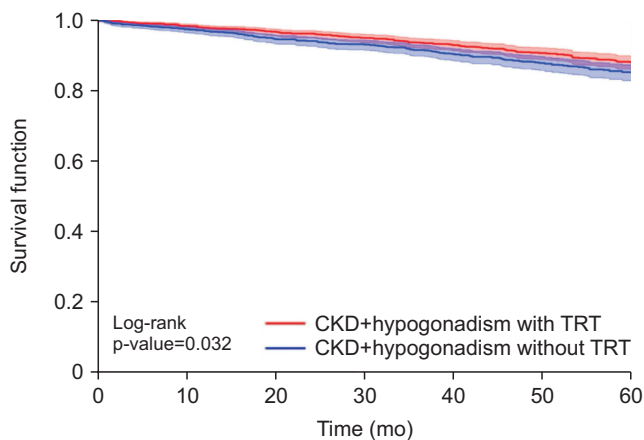
### 1. Outcomes

The median follow-up duration was 60 months (interquartile range, IQR 29) in the testosterone-treated cohort and 45 months (IQR 41) in the untreated cohort.

To account for this difference, we used time-to-event analyses. Kaplan–Meier survival curves were generated to compare survival between groups, and Cox proportional hazards models were used to estimate adjusted HRs. The proportional hazards assumption was formally tested and satisfied, supporting the validity of the survival comparisons.

In the matched cohort analysis, testosterone treatment was associated with significantly improved survival. Kaplan–Meier analysis demonstrated a higher survival probability in the treated cohort over time (log-rank  $p=0.032$ ). In the Cox model, testosterone treatment was associated with a 22% lower hazard of death (HR: 0.78; 95% CI 0.63 to 0.98) (Fig. 2).

In the matched cohorts, under the proportional hazards assumption, there were no statistically significant differences between the TRT and non-TRT groups for any secondary outcome (Table 4).



**Fig. 2.** Survival function in the two groups over the space of 5 years. In red patients with hypogonadism receiving TRT, and in blue patients with hypogonadism not on TRT. The index event refers to the commencement of TRT for the treated patients (red curve) and to the diagnosis of hypogonadism for the untreated patients (blue curve). TRT: testosterone replacement therapy, CKD: chronic kidney disease.

### 1) Subgroup analysis results

After matching, subgroup sizes were 581 *vs.* 581 for CKD stage 3a, 277 *vs.* 277 for advanced non-dialysis CKD (stages 3b to 5, eGFR 10 to 44 mL/min/1.73 m<sup>2</sup>), and 139 *vs.* 139 for dialysis (Table 5). In CKD stage 3a, TRT was associated with lower all-cause mortality (2.58% *vs.* 5.16%; risk ratio [RR] 0.50, 95% CI 0.27 to 0.92; HR 0.46, 95% CI 0.25 to 0.86), with no significant differences for VaD, stroke, myocardial infarction, heart failure, or prostate cancer. In the advanced CKD subgroup, mortality was likewise lower in TRT-treated patients (11.91% *vs.* 19.49%; RR 0.61, 95% CI 0.41 to 0.91; HR 0.55, 95% CI 0.36 to 0.85), whereas other outcomes did not differ significantly; results for AD and prostate neoplasia were suppressed by TriNetX because of low event counts. Among dialysis patients, TRT was also associated with significantly reduced mortality (26.62% *vs.* 35.97%; HR 0.54, 95% CI 0.35 to 0.83), while stroke risk was similar between groups; several outcomes, notably dementia, myocardial infarction and prostate cancer, had too few events for reliable estimation. Interaction testing did not identify significant modification of the TRT–mortality association by CKD severity or dialysis status (Table 5).

## DISCUSSION

Some symptoms improve with TRT, which can enhance sexual function, mood, and muscle mass. CKD patients are not commonly prescribed TRT as shown in this study (32.2% of those found to have hypogonadism treated *vs.* 67.8% untreated). This may be due to various associated health concerns, especially from the cardiovascular perspective.

This propensity score–matched analysis of hypogonadal males with CKD stages 3 to 5 found that TRT

**Table 4.** Percentage of patients with secondary outcome and hazard ratio (95% CI)

Outcome	TRT %	Non-TRT %	Risk difference % (95% CI)	Hazard ratio (95% CI)	p-value
Vascular dementia	4.34	3.88	0.45 (-0.95, 1.85)	0.96 (0.68, 1.36)	0.411
Alzheimer's disease	0.91	0.65	0.26 (-0.36, 0.88)	1.51 (0.63, 3.60)	0.356
Stroke	12.56	12.03	0.53 (-1.95, 3.02)	0.89 (0.72, 1.10)	0.576
Myocardial infarction	8.18	6.76	1.42 (-0.51, 3.35)	1.04 (0.79, 1.36)	0.765
Prostate-related conditions	3.04	3.53	-0.49 (-1.75, 0.78)	0.75 (0.51, 1.11)	0.154
Prostate cancer	2.98	3.59	-0.61 (-1.87, 0.65)	0.72 (0.49, 1.07)	0.143
Heart failure	15.31	14.13	1.18 (-1.53, 3.89)	0.93 (0.76, 1.13)	0.921

CI: confidence interval, TRT: testosterone replacement therapy.

**Table 5.** Stratified association between TRT and clinical outcomes across CKD severity categories and dialysis status after propensity-score matching

Subgroup	Matched sample size, n (TRT vs. non-TRT)	Mortality risk, % (TRT vs. non-TRT)	Risk ratio (95% CI)	Hazard ratio (95% CI)	Other outcome
CKD stage 3a	581 vs. 581	2.58 vs. 5.16	0.50 (0.27–0.92)	0.46 (0.25–0.86)	No significant differences for vascular dementia, stroke, MI, or HF. Alzheimer's disease and prostate-related outcomes suppressed due to low event counts
CKD stage 3b–5 (eGFR 10–44 mL/min/1.73 m <sup>2</sup> )	277 vs. 277	11.91 vs. 19.49	0.61 (0.41–0.91)	0.55 (0.36–0.85)	No significant differences for vascular dementia, stroke, MI, or HF. AD and prostate outcomes suppressed due to low event counts
Dialysis patients	139 vs. 139	26.62 vs. 35.97	0.74 (0.52–1.05)	0.54 (0.35–0.83)	Stroke risk similar. Dementia, MI, and prostate outcomes suppressed due to very low event counts

Subgroup analyses were performed on a separate TriNetX query run; patient counts differ slightly from the primary cohort.

Interaction testing did not demonstrate significant modification of TRT effects by CKD severity or dialysis status.

Several outcomes were suppressed due to low cell counts (<10 events).

TRT: testosterone replacement therapy, CKD: chronic kidney disease, CI: confidence interval, MI: myocardial infarct, HF: hearth failiure, AD: Alzheimer's disease.

was associated with a significantly lower risk of all-cause mortality with a HR of 0.78 (95% CI 0.63 to 0.98) compared to those who did not receive TRT.

The potential survival benefit we observed may be mediated through several mechanisms. Hypogonadism is associated with increased frailty, anemia, inflammation, and impaired cardiovascular health, all of which are prevalent and prognostically important in CKD. TRT can partially counteract harmful pathways in CKD related hypogonadism by acting on various biological systems [26]. It decreases systemic inflammation by reducing pro-inflammatory cytokines and NF-κB signaling, which helps prevent vascular damage and muscle breakdown [27]. TRT boosts insulin sensitivity by increasing lean muscle mass, decreasing visceral fat, and improving insulin signaling [28], and it positively influences lipid metabolism by lowering low-density lipoprotein cholesterol and triglycerides while increasing HDL [29]. TRT promotes the production of red blood cells by raising erythropoietin levels and suppressing hepcidin [30], aiding in anemia correction. In skeletal muscle, testosterone stimulates protein synthesis through mTOR pathways and reduces protein breakdown, thereby enhancing muscle mass and strength [31]. Finally, TRT benefits vascular health via direct vasodilation [32]. TRT may partially reverse these detrimental pathways, improving metabolic health, physical function, and overall resilience. Notably, our study extends prior work on TRT in general populations by

focusing on non-transplant CKD stage 3 to 5 patients, a group for whom evidence is lacking.

Secondary outcomes, including VaD, AD, stroke, myocardial infarction, prostate-related conditions, prostate cancer, and heart failure, did not differ significantly between the TRT and non-TRT cohorts. This suggests that TRT use in advanced CKD patients did not confer an increased risk of major cardiovascular or prostate-cancer adverse events.

While earlier studies indicated that testosterone has neuroprotective effects, our results did not show a reduced risk of dementia diagnosis in CKD may be due to inconsistent and inaccurate testing for dementia among these patients, competing with the effects of CKD, which might negate this potential benefit.

Finally, the risk of cardiovascular events and prostate cancer was not significantly higher among CKD TRT users, alleviating previous concerns about prescribing testosterone therapy.

Importantly, stratified analyses by CKD stage and dialysis status suggested that the observed mortality benefit with TRT was broadly consistent from stage 3a through advanced CKD and dialysis, with no statistically significant interaction by CKD severity, although power was limited for non-mortality endpoints and some outcomes in advanced CKD subgroups were under-represented or suppressed because of small numbers.

This study emphasizes that even within the CKD context, TRT can be used to alleviate symptoms of hy-

hypogonadal males and may have a beneficial impact on their life span, despite the CKD burden. Our analysis shows the underutilization of TRT despite the diagnosis of hypogonadism. To our knowledge, this is the first work to examine TRT in CKD and dialysis patients, using a large real-world dataset. Another strength of our study is that we establish a clear temporal relationship between the formal diagnosis of hypogonadism and the start of TRT, reducing variability in therapy initiation.

**Limitations:** the retrospective nature of our study design restricts the ability to infer causality. Additionally, the follow-up period may not be sufficient to assess long-term cognitive effects. This study may be subject to residual confounding, misclassification due to diagnostic coding, incomplete data on TRT regimen and adherence, as well as variations in testosterone formulations and dosage regimens. Assessing TRT effectiveness in terms of biochemical or symptomatic response was not feasible in TriNetX due to inconsistent availability of testosterone levels, symptom scores, or medication adherence data. The analysis captures treatment initiation but not effectiveness or treatment continuation, which are common limitations in real-world EHR data studies. Subclinical hypogonadism was not identified because it is not coded in TriNetX. The effective sample size for the detection of subtypes of dementia was likely too low to detect small differences between groups.

## CONCLUSIONS

Our findings are the first to suggest that TRT is associated with reduced mortality rates, with no increase in risk of prostate cancer or cardiovascular risk in CKD cohorts, potentially alleviating concerns about its safety in CKD populations. These results could have a significant impact on hypogonadal CKD patients (including recent dialysis starters), who already experience a low QoL due to the chronicity of their disease and treatments, and in whom TRT is highly underutilized. These findings support the need for more widespread assessment of gonadal function in men with CKD, and consideration of routine testing as part of comprehensive care.

## Conflict of Interest

LM, MJK, GGB have nothing to disclose. SW and FRu are

employed by TriNetX, LLC. The research was conducted without any commercial or financial relationships that could be perceived as a potential conflict of interest. FR is on the advisory board for Alnylam. JT received consulting fees from AstraZeneca and the Royal College of GPs, honoraria from AstraZeneca and Bayer, support for attending meetings from Bayer, and consulting fees from Boehringer Ingelheim. RAD received grants from NIH, Alzheimer's Society and Lilly. Received consulting fees and honoraria from Lilly, is on advisory board for Otsuka. GH occasional adviser for Besins and Grunenthal Ltd. PAK received grants from Vifor, Astellas, Pharmacosmos, and Unicyte. Received consulting fees and honoraria from Vifor, AstraZeneca, Pfizer, Pharmacosmos, Napp, GSK, Novartis, Bayer. Received consulting fees from AstraZeneca, Vifor, Unicyte, UCB, and Otsuka. Received support for attending meetings from Pharmacosmos, Vifor, and Medice.

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## Author Contribution

Conceptualization: LM. Data curation: LM. Formal analysis: LM. Investigation: LM. Methodology: LM, Francesco Rainone, JT. Project administration: PAK. Resources: GGB, Francesca Rusconi. Supervision: PAK, RAD, GH. Validation: SW. Visualization: LM, MJK. Writing – original draft: LM, MJK. Writing – review & editing: LM, Francesco Rainone, JT, Francesca Rusconi, RAD, GH, PAK.

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