CLINICAL RESEARCH STUDY

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Cardiovascular and Cerebrovascular Safety of Testosterone Replacement Therapy Among Aging Men with Low Testosterone Levels: A Cohort Study

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ABSTRACT

PURPOSE: We assessed the risk of ischemic stroke, transient ischemic attack, and myocardial infarction associated with testosterone replacement therapy (TRT) among aging men with low testosterone levels.

METHODS: Using the UK Clinical Practice Research Datalink, we formed a cohort of men aged 45 years or older with low testosterone levels and no evidence of hypogonadotropic or testicular disease, between 1995 and 2017. Hazard ratios (HRs) and 95% confidence intervals (CIs) of a composite of ischemic stroke/transient ischemic attack and myocardial infarction were estimated using time-dependent Cox proportional hazards models, comparing current use of TRT with nonuse.

RESULTS: The cohort included 15,401 men. During 71,541 person-years of follow-up, 850 patients experienced an ischemic stroke/transient ischemic attack/myocardial infarction (crude incidence rate 1.19 [95% confidence interval (CI), 1.11-1.27] per 100 persons per year). Compared with nonuse, current use of TRT was associated with an increased risk of the composite outcome (HR 1.21; 95% CI, 1.00-1.46). This risk was highest in the first 6 months to 2 years of continuous TRT use (HR 1.35; 95% CI, 1.01-1.79), as well as among men aged 45-59 years (HR 1.44; 95% CI, 1.07-1.92).

CONCLUSIONS: TRT may increase the risk of cardiovascular events in aging men with low testosterone levels, particularly in the first 2 years of use. In the absence of identifiable causes of hypogonadism, TRT should be initiated with caution among aging men with low testosterone levels.

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KEYWORDS: Hypogonadism; Myocardial infarction; Stroke; Testosterone replacement therapy

INTRODUCTION

Testosterone replacement therapy (TRT) is used for the treatment of male testosterone deficiency, or hypogonadism.[1] While the rates of hypogonadism have remained stable, TRT prescriptions have increased by over threefold from 2001 to 2011 in the United States,[2,3] and by almost 90% from 2001 to 2010 in the United Kingdom.[4] Thus, TRT may be increasingly prescribed to relieve nonspecific symptoms of aging, such as fatigue and declining sexual function. While

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endogenous testosterone levels are known to decrease modestly with age, the clinical benefits of TRT in late-onset hypogonadism are moderate, at best.[5] Consequently, TRT is not indicated among aging, but otherwise healthy, men.[6,7]

In addition to the unclear benefits of TRT among aging men with testosterone decline, concerns have emerged as to the cardiovascular and cerebrovascular safety of these medications. While randomized controlled trials (RCTs) have not been sufficiently powered to detect differences in the rates of adverse vascular events comparing testosterone with placebo,[8] observational studies have generated conflicting findings. Indeed, some have reported an increased risk of stroke or myocardial infarction associated with TRT,[9,10] whereas others have reported the opposite association, with testosterone having a strong protective effect.[11,12] Given these uncertainties, different federal and regulatory agencies have also adopted different standpoints. For example, the US Food and Drug Administration and Health Canada have issued warnings as to the potential risks associated with TRT, while the European Medicines Agency has found no consistent evidence for such risks.[6,7,13] The US and European Endocrine Society recently acknowledged a lack of conclusive evidence and the need for additional information about the cardiovascular safety of TRT.[14,15]

CLINICAL SIGNIFICANCE

- Current use of testosterone replacement therapy among aging men with low testosterone levels was associated with an increased risk of a composite of ischemic stroke, transient ischemic attack, and myocardial infarction.
- The association was highest in the first 2 years of use.
- In aging men, the potential cardiovascular risk of testosterone replacement therapy should be weighed against its expected benefits.

In light of the ongoing uncertainty about the cardiovascular safety of these medications, the objective of this population-based study was to evaluate the association between TRT and the risk of ischemic stroke/transient ischemic attack and myocardial infarction, in aging men with low testosterone levels.

METHODS

Data Source

This study was conducted using the Clinical Practice Research Datalink (CPRD). This database contains electronic medical records of more than 15 million patients enrolled in over 700 primary care practices in the UK.[16–18] The information collected includes demographic data and lifestyle habits, diagnoses, and referrals to specialists and hospitals. Data related to medical diagnoses, procedures, and services are coded using the Read classification scheme,[19] while prescriptions are recorded using the UK's *Dictionary of Medicines and Devices*.[20] In CPRD practices, prescriptions issued by general practitioners are automatically transcribed into patients' electronic records. Quality control is performed regularly, and numerous studies have shown the validity and high quality of the recorded data.[21,22]

The study protocol (No. 17_274) was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Committee of the Jewish General Hospital (Montreal, Canada).

Study Population

We identified a cohort of all men, aged 45 years or older, diagnosed with low testosterone levels between January 1, 1995 and August 31, 2017. A low testosterone level was defined on the basis of laboratory test values indicating low levels of serum or free testosterone using reference ranges set by the individual laboratories, or relevant Read codes for a diagnosis for hypogonadism. In the event that a patient had both a diagnosis and a laboratory value, the earliest qualifying event was considered the date of cohort entry. We excluded patients with <12 months of registration with the CPRD prior to cohort entry, as well as patients with a history of TRT use at any time prior to cohort entry (to maximize the inclusion of new users in the cohort). We also excluded patients with a history of prostate cancer or androgen deprivation therapy, as these represent contraindications to TRT. Finally, patients with known causes of hypogonadism prior to cohort entry, such as diseases of the testes and the hypothalamic-pituitary axis, were also excluded. All patients were followed starting from cohort entry until occurrence of the outcome of interest, incident diagnosis of prostate cancer or receipt of androgen deprivation therapy, death from any cause, end of registration with the practice, or end of the study period (August 31, 2017), whichever occurred first.

Exposure Definition

We identified all prescriptions of TRT during follow-up from the computerized medical records. Using a time-varying exposure definition, for each patient, each day of follow-up was classified into one of the following mutually exclusive categories: current use of TRT defined by the intended duration of each prescription plus a 30-day grace period (to account for refill time or residual treatment effects); past use, defined as no current use but evidence of use in the previous 60 days; and nonuse otherwise. Nonuse was the reference category.

Outcome Definition

The primary outcome of interest was a composite of myocardial infarction (including acute ST-segment elevation and non-ST-segment elevation myocardial infarction) and ischemic stroke/transient ischemic attack, which were also assessed as individual outcomes. Read codes for identifying each of these events in the CPRD have been validated.[22–24] We also evaluated the risk of all-cause mortality as a secondary outcome.

Potential Confounders

All models were adjusted for the following potential confounding variables: age, calendar year of cohort entry, body mass index (BMI), smoking status, alcohol abuse, hyperlipidemia, hypertension, diabetes, atrial fibrillation, coronary artery disease, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, history of ischemic stroke/transient ischemic attack, chronic kidney disease, cancer (other than nonmelanoma skin cancer), liver disease, obstructive sleep apnea, venous thromboembolism, use of anticoagulants, antiplatelets, nonsteroidal anti-inflammatory drugs, antipsychotics, antidepressants, number of physician visits as measure of health utilization, and number of prescribed medications as a surrogate marker for overall health. All covariates were identified in the year prior to cohort entry, with the exception of BMI and smoking status, which were measured in the 5 years prior.

Statistical Analyses

Descriptive statistics were used to present the baseline characteristics of the study cohort. Crude incidence rates and 95% confidence intervals (CIs) of outcome events were estimated based on the Poisson distribution. In primary analyses, we used time-dependent Cox proportional hazards models, adjusted for the aforementioned covariates, to estimate hazard ratios (HRs) and 95% CIs of ischemic stroke/transient ischemic attack and myocardial infarction associated with current use of TRT compared with nonuse.

In secondary analyses, we assessed whether there was a duration–response relation between current TRT use and ischemic stroke/transient ischemic attack and myocardial infarction, by estimating HRs for predefined categories of continuous duration of use (<6 months, 6 months-2 years, and >2 years). We also used a restricted cubic spline with 5 interior knots to produce a smooth curve of the HR as a function of duration of TRT use. Finally, we determined whether the risk varied with TRT formulation (gel/cream, implant/injection, oral, patch), patient age (45-59, 60-74, and ≥75 years), and patient history of cardiovascular disease using 2 different definitions, first including a history of ischemic stroke/transient ischemic attack, or coronary artery disease, and second including a history of ischemic stroke/transient ischemic attack, coronary artery disease, atrial fibrillation, or heart failure. In separate models, we also assessed whether there was an association between current TRT use and all-cause mortality.

Several sensitivity analyses were performed in order to verify the robustness of our results. First, we used marginal structural Cox proportional hazards models to explore the impact of time-dependent confounding (Supplementary Methods 1, available online).[25] Second, we modified our definition of current, past, and nonuse of TRT, so as to explore different potential etiologic exposure windows, as well as the extent of any exposure misclassification (Supplementary Methods 2, available online). Third, we repeated analyses considering patients unexposed from cohort entry until first TRT prescription, and exposed thereafter until the end of follow-up, analogous to an intention-to-treat approach. This allowed for an assessment of the potential for reverse causality, particularly for the mortality outcome, wherein TRT may be discontinued in patients with a perceived risk of death in the near future, leading to an artificially lower risk of mortality associated with current TRT use. Fourth, we repeated the primary analysis using multiple imputation for variables with missing data (ie, BMI and smoking status). Finally, to further explore the potential for reverse causality in the association between TRT and all-cause mortality, we repeated the analysis using 5-alpha-reductase (5AR) inhibitors overall and finasteride as negative control exposures. Indeed, these drugs have no known effect on the risk of all-cause mortality and may also be discontinued in patients with a perceived risk of death in the near future.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

After applying all exclusion criteria, our final cohort comprised 15,401 hypogonadal men (Figure 1) with a mean age of 60.4 years (standard deviation [SD] 9.6 years) (Table 1). TRT was prescribed to 4485 patients (29.1%) on at least one

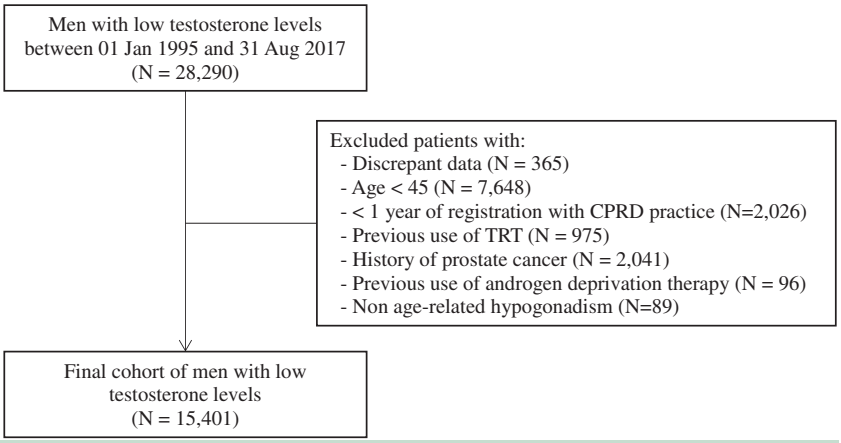

Figure 1 Cohort definition flowchart. **Figure 1** CPRD = Clinical Practice Research Datalink; TRT = testosterone replacement therapy.

Table 1 Baseline Characteristics of Men with Low Testosterone Levels Included in the Study Cohort

	All Patients (n = 15,401)	TRT Use Within 90 Days of Cohort Entry	
		Use (n = 2237)	No Use (n = 13,164)
Age, years, mean (SD)	60.4 (9.6)	60.0 (9.2)	60.4 (9.7)
45-54	4859 (31.5)	720 (32.2)	4139 (31.4)
55-64	5531 (35.9)	809 (36.2)	4722 (35.9)
65-74	3676 (23.9)	552 (24.7)	3124 (23.7)
75-84	1163 (7.6)	138 (6.2)	1025 (7.8)
85	172 (1.1)	18 (0.8)	154 (1.2)
Comorbidities and risk factors			
Body mass index			
30	5850 (38.0)	864 (38.6)	4986 (37.9)
25-29	4464 (29.0)	653 (29.2)	3811 (29.0)
<25	1654 (10.7)	233 (10.4)	1421 (10.8)
Unknown	3433 (22.3)	487 (21.8)	2946 (22.4)
Smoking status			
Never	4471 (29.0)	643 (28.7)	3828 (29.1)
Ever	9422 (61.2)	1379 (61.6)	8043 (61.1)
Unknown	1508 (9.8)	215 (9.6)	1293 (9.8)
Alcohol abuse	197 (1.3)	22 (1.0)	175 (1.3)
Hyperlipidemia	6782 (44.0)	1038 (46.4)	5744 (43.6)
Hypertension	7636 (49.6)	1117 (49.9)	6519 (49.5)
Diabetes	3726 (24.2)	573 (25.6)	3153 (24.0)
Atrial fibrillation	209 (1.4)	19 (0.8)	190 (1.4)
Coronary artery disease	914 (5.9)	142 (6.3)	772 (5.9)
Congestive heart failure	121 (0.8)	11 (0.5)	110 (0.8)
Peripheral vascular disease	93 (0.6)	14 (0.6)	79 (0.6)
COPD	639 (4.1)	91 (4.1)	548 (4.2)
Ischemic stroke/TIA	119 (0.8)	12 (0.5)	107 (0.8)
Venous thromboembolism	107 (0.7)	24 (1.1)	83 (0.6)
Chronic kidney disease	4552 (29.6)	627 (28.0)	3925 (29.8)
Cancer	239 (1.6)	66 (1.0)	124 (1.9)
Liver disease	67 (0.4)	34 (0.4)	30 (0.5)
Obstructive sleep apnea	114 (0.7)	65 (0.9)	45 (0.7)
Medications			
Anticoagulants	710 (4.6)	98 (4.4)	612 (4.6)
Antiplatelets	3828 (24.9)	566 (25.3)	3262 (24.8)
NSAIDs	3873 (25.1)	603 (27.0)	3270 (24.8)
Antipsychotics	748 (4.9)	128 (5.7)	620 (4.7)
Antidepressants	3514 (22.8)	629 (28.1)	2885 (21.9)
Other medications			
0	807 (5.2)	108 (4.8)	699 (5.3)
1-5	5809 (37.7)	767 (34.3)	5042 (38.3)
6-10	4393 (28.5)	615 (27.5)	3778 (28.7)
10	4392 (28.5)	747 (33.4)	3645 (27.7)
Physician visits			
0	4373 (28.4)	571 (25.5)	3802 (28.9)
1-5	6267 (40.7)	881 (39.4)	5386 (40.9)
6-10	2431 (15.8)	380 (17.0)	2051 (15.6)
11	2330 (15.1)	405 (18.1)	1925 (14.6)

All values are presented as n (%), unless otherwise stated.

COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation; TIA = transient ischemic attack; TRT = testosterone replacement therapy.

The 2,237 TRT users in the first 90 days represent 49.8% of all patients eventually exposed during the entire follow-up.

occasion during a mean follow-up time of 4.7 years (SD 3.7 years), with a majority of patients initiated on testosterone gels/creams (56.8%) and injections (33.6%).

Overall, 850 patients experienced an ischemic stroke/transient ischemic attack or myocardial infarction during 71,541 person-years of follow-up, yielding a crude incidence rate of

Table 2 Crude and Adjusted Hazard Ratios of Stroke/Transient Ischemic Attack and Myocardial Infarction Associated with the Use of Testosterone Replacement Therapy

Exposure	Events	Person-Years	Incidence Rate (95% CI)	Crude HR	Adjusted HR (95% CI)
Composite of ischemic stroke/TIA/myocardial infarction					
Nonuse	711	61,023	1.17 (1.08-1.25)	1.00	1.00 (Reference)
Current TRT use	128	9474	1.35 (1.14-1.61)	1.16	1.21 (1.00-1.46)
<6 months	57	4056	1.41 (1.08-1.82)	1.19	1.21 (0.92-1.59)
6 months-2 years	52	3496	1.49 (1.13-1.95)	1.31	1.35 (1.01-1.79)
>2 years	19	1922	0.99 (0.63-1.55)	0.86	0.93 (0.59-1.48)
Past TRT use	11	1044	1.05 (0.58-1.90)	0.90	0.91 (0.50-1.66)
Ischemic stroke/TIA					
Nonuse	440	62,043	0.71 (0.65-0.78)	1.00	1.00 (Reference)
Current TRT use	78	9611	0.81 (0.65-1.01)	1.13	1.23 (0.96-1.57)
<6 months	36	4103	0.88 (0.63-1.22)	1.21	1.28 (0.91-1.81)
6 months-2 years	30	3544	0.85 (0.59-1.21)	1.18	1.28 (0.88-1.86)
>2 years	12	1964	0.61 (0.35-1.08)	0.88	1.02 (0.57-1.82)
Past TRT use	9	1060	0.85 (0.44-1.63)	1.19	1.23 (0.63-2.38)
Myocardial infarction					
Nonuse	302	62,437	0.48 (0.43-0.54)	1.00	1.00 (Reference)
Current TRT use	54	9656	0.56 (0.43-0.73)	1.19	1.17 (0.87-1.57)
<6 months	24	4120	0.58 (0.39-0.87)	1.22	1.19 (0.78-1.82)
6 months-2 years	23	3564	0.65 (0.43-0.97)	1.45	1.41 (0.92-2.18)
>2 years	7	1971	0.36 (0.17-0.74)	0.71	0.72 (0.34-1.54)
Past TRT use	S	S	0.28 (0.09-0.87)	0.60	0.59 (0.19-1.83)

CI = confidence interval; HR = hazard ratio; TIA = transient ischemic attack; TRT = testosterone replacement therapy.
Incidence rates are expressed per 100 persons per year.
Adjusted for all variables listed in Table 1.
Cells with <5 events or with possibility of unintentional (deductive) disclosure were suppressed owing to privacy restrictions, in accordance with Clinical Practice Research Datalink policy.

1.19 per 100 persons per year (95% CI, 1.11-1.27). Current use of TRT was associated with a 21% increased risk of a composite of ischemic stroke/transient ischemic attack/myocardial infarction compared with nonuse (HR 1.21; 95% CI, 1.00-1.46) (Table 2), corresponding to an adjusted risk difference of 2.4 events per 1000 persons per year. This rate was highest in the first 6 months to 2 years of continuous TRT use (HR 1.35; 95% CI, 1.01-1.79), and decreased thereafter (Table 2 and Supplementary Figure 1). This rate was also higher among patients aged 45-59 years (HR 1.44; 95% CI, 1.07-1.92) (Supplementary Table 1), and was increased in patients with and without prior cardiovascular disease, although the

Table 3 Crude and Adjusted Hazard Ratios of Ischemic Stroke/Transient Ischemic Attack/Myocardial Infarction Associated with the Use of TRT, Stratified by History of Stroke/Transient Ischemic Attack/Coronary Artery Disease

Patient Subgroup	Events	Person-Years	Incidence Rate (95% CI)	Crude HR	Adjusted HR (95% CI)
No history of ischemic stroke/TIA/CAD					
Nonuse	623	57,295	1.09 (1.01-1.18)	1.00	1.00 (Reference)
Current TRT use	110	8890	1.24 (1.03-1.49)	1.14	1.18 (0.96-1.45)
Past TRT use	S	S	0.72 (0.34-1.50)	0.66	0.66 (0.31-1.40)
History of ischemic stroke/TIA/CAD					
Nonuse	88	3729	2.36 (1.92-2.91)	1.00	1.00 (Reference)
Current TRT use	18	584	3.08 (1.94-4.89)	1.33	1.56 (0.93-2.63)
Past TRT use	S	S	5.86 (2.20-15.61)	2.50	2.78 (1.00-7.67)

CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; TIA = transient ischemic attack; TRT = testosterone replacement therapy.
Incidence rates are expressed per 100 persons per year.
Adjusted for all variables listed in Table 1.
Cells with < 5 events or with possibility of unintentional (deductive) disclosure were suppressed owing to privacy restrictions, in accordance with Clinical Practice Research Datalink policy.

Table 4 Crude and Adjusted Hazard Ratios of Ischemic Stroke/Transient Ischemic Attack/Myocardial Infarction Associated with the Use of TRT, Stratified by History of Stroke/Transient Ischemic Attack/Coronary Artery Disease/Atrial Fibrillation/Heart Failure

Patient Subgroup	Events	Person-Years	Incidence Rate (95% CI)	Crude HR	Adjusted HR (95% CI)
No history of ischemic stroke/TIA/CAD/AF/HF					
Nonuse	602	56,576	1.06 (0.98-1.15)	1.00	1.00 (Reference)
Current TRT use	110	8795	1.25 (1.04-1.51)	1.18	1.21 (0.98-1.48)
Past TRT use	S	S	0.73 (0.35-1.52)	0.69	0.69 (0.33-1.46)
History of ischemic stroke/TIA/CAD/AF/HF					
Nonuse	109	4447	2.45 (2.03-2.96)	1.00	1.00 (Reference)
Current TRT use	18	678	2.65 (1.67-4.21)	1.09	1.20 (0.72-1.99)
Past TRT use	S	S	5.00 (1.88-13.31)	1.97	2.08 (0.76-5.71)

AF = atrial fibrillation; CAD = coronary artery disease; CI = confidence interval; HF = heart failure; HR = hazard ratio; TIA = transient ischemic attack; TRT = testosterone replacement therapy.

Incidence rates are expressed per 100 persons per year.

Adjusted for all variables listed in Table 1.

Cells with <5 events or with possibility of unintentional (deductive) disclosure were suppressed owing to privacy restrictions, in accordance with Clinical Practice Research Datalink policy.

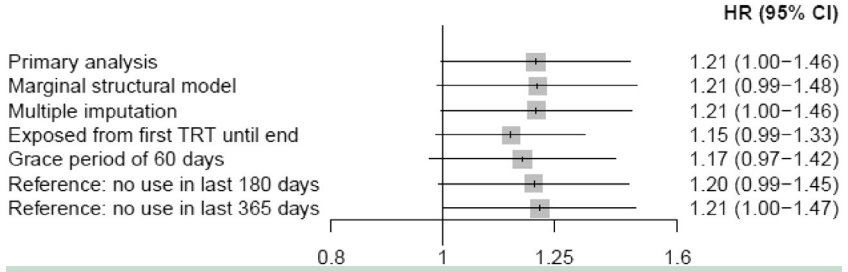

Figure 2 Forest plot with results of the primary and sensitivity analyses evaluating the risk of ischemic stroke/transient ischemic attack/myocardial infarction associated with current testosterone replacement therapy use compared with nonuse. **Figure 2** CI = confidence interval; HR = hazard ratio.

results did not reach statistical significance (Tables 3 and 4). No differences were observed when current use was stratified by TRT formulation, although the number of events was low in some strata (Supplementary Table 2). The results of the primary analyses were virtually unchanged across multiple sensitivity analyses (Figure 2).

The risk of all-cause mortality was significantly lower with current TRT use (HR 0.64; 95% CI, 0.52-0.78) and higher with past TRT use (HR 1.72; 95% CI, 1.21-2.45), compared with nonuse (Table 5). Results were consistent in subgroup and sensitivity analyses (Supplementary Tables 3-6). Similarly, in supplementary analyses using 5AR inhibitors or finasteride as negative control exposures, current use was also associated with a lower risk of all-cause mortality, while past use was associated with an increased risk compared with nonuse, although results were not statistically significant (Supplementary Table 7). As expected, these same negative control exposures were not associated with the rate of the composite of ischemic stroke/transient ischemic attack/myocardial infarction (data not shown).

Table 5 Crude and Adjusted Hazard Ratios of All-Cause Mortality Associated with the Use of Testosterone Replacement Therapy

Exposure	Events	Person-Years	Incidence Rate (95% CI)	Crude HR	Adjusted HR (95% CI)
Nonuse	1168	63,512	1.84 (1.74-1.95)	1.00	1.00 (Reference)
Current TRT use	98	9801	1.00 (0.82-1.22)	0.56	0.64 (0.52-0.78)
Past TRT use	32	1082	2.96 (2.09-4.18)	1.66	1.72 (1.21-2.45)

CI = confidence interval; HR = hazard ratio; TRT = testosterone replacement therapy.

Incidence rates are expressed per 100 persons per year.

Adjusted for all variables listed in Table 1.

DISCUSSION

In this population-based cohort study of aging men with low testosterone levels, current exposure to TRT was associated with an increased risk of ischemic stroke/transient ischemic attack/myocardial infarction. This association was highest in the first 2 years after treatment initiation, as well as among middle-aged patients, although a similar increased risk in older patients is possible. Conversely, current use of TRT was associated with a decreased risk of mortality and past use with an increased risk, suggesting that this protective effect on mortality was likely due to reverse causality.

Concerns with regards to the safety of TRT were first widespread after publication of the findings of the Testosterone in Older Men trial, which was discontinued owing to a higher number of adverse cardiovascular events in the TRT group compared with the placebo group,[26] but other RCTs did not show similar differences.[27–29] However, existing RCTs have not been sufficiently powered to detect potential associations between TRT and vascular events, due to both small sample sizes and short follow-up time. Moreover, subsequent meta-analyses have generated inconsistent findings, partly due to the limitations of the included RCTs.[8] While the rates of TRT increased substantially in the early 2000s, these cardiovascular concerns may explain the decrease in use that has been observed recently in the US.[30]

To date, several observational studies have investigated the association between TRT and cardiovascular risk, with conflicting results that can be ascribed to several reasons. First, as discussed previously,[31] methodologic limitations such as potential exposure misclassification leading to immortal time bias may explain some previous findings of a strong protective effect of TRT on the risk of cardiovascular events.[11,12] Second, the different findings may have resulted from the study of distinct populations. For example, some cohorts included all hypogonadal men, irrespective of the underlying cause (ie, included men that have hypogonadism due to an underlying structural, congenital, or destructive disorder affecting the hypothalamus, pituitary, or testes, leading to permanent hypogonadism that may also present at an earlier age),[12,32] while others included all men, with or without hypogonadism.[10,33,34] Still others were restricted to men with a high baseline cardiovascular risk.[9] We found an increased risk of a composite outcome of ischemic stroke/transient ischemic attack/myocardial infarction as well as cerebrovascular and cardiovascular events separately, although the study was underpowered to reach statistical significance. Third, as shown in our study, TRT may heighten the risk of vascular events only transiently, within the 2 years after initiation and with little effect thereafter, likely due to the phenomenon of depletion of susceptibles.[35] A similar transient increased risk was reported for the association between TRT and venous thromboembolism.[36] Regarding the risk of arterial vascular events, this duration–response relation was suggested in one meta-analysis of RCTs,[37] but has been explored in only one observational study. One previous study reported an elevated risk of myocardial infarction among current new users of TRT, however, the risk with duration of TRT use was not assessed.[33] In another publication, TRT increased the risk of cardiovascular events within the first 18 months of initiation, and was protective with longer duration of exposure.[34] However, this analysis may have been influenced by immortal time bias, as treated patients must have remained event-free prior to contributing to the higher strata of cumulative exposure. We also showed that the risk of cardio- and cerebrovascular events was mostly driven by a heightened risk in middle-aged men. The risk was also slightly increased in those aged 60 to 74 years, but the results did not reach statistical significance. However, the upper bound of the 95% CI indicates that a risk as high as 57% cannot be ruled out. There was no clear evidence of an increased risk in the elderly, an effect that may be due to preferential prescribing to healthier patients. Moreover, the number of patients exposed in this age group was low, precluding any firm conclusion about the cardiovascular risk associated with TRT in this age group. Finally, the HR associated with current use of TRT was elevated in patients with and without cardiovascular disease, regardless of the definition used to define history of cardiovascular disease. Indeed, the confidence intervals for these analyses were overlapping. As this was a secondary analysis based on fewer events, additional studies with larger sample size will be needed to assess this effect modification by prior cardiovascular disease.

The mechanism for the effect of exogenous testosterone on the cardiovascular and cerebrovascular system is complex, and remains to be well established.[38] Testosterone has been observed to enhance platelet aggregation,[39] which may increase the risk of ischemic stroke/transient ischemic attack and myocardial infarction by contributing to coronary plaque and thrombus development.[40] In the recent Cardiovascular Trial of the Testosterone Trials, TRT also significantly increased coronary artery plaque volume among elderly hypogonadal men after 1 year of treatment,[41] raising additional concerns as to the risk of coronary atherosclerosis and acute coronary syndrome in this population. Exogenous testosterone has also been associated with polycythemia and erythrocytosis,[42,43] which may also play a role in heightening the risk of thrombotic events.[44] Finally, it has been suggested that TRT may impart cardiovascular risks by inducing or exacerbating obstructive sleep apnea.[45,46]

The protective effect of TRT on all-cause mortality in our study is surprising, given the concurrent increased risk of vascular events. However, the similar pattern of risk observed with 5AR inhibitors and finasteride suggests the influence of certain biases, because these medications are not known to be associated with mortality. Specifically, the protective effect may be the result of reverse causality, in which physicians may discontinue TRT based on perceived deterioration of health or imminent death, because TRT is not a vital medication. In accordance with this hypothesis, past TRT use was associated with a high mortality risk compared with nonuse. Moreover, TRT may be less frequently initiated among men with a higher baseline risk of mortality, particularly in the elderly, and those who did receive TRT may have been overall healthier compared with their untreated counterparts. This may explain the

small number of patients aged 75 years or older initiating TRT in our cohort, as well as the protective effect of TRT on all outcomes events among these elderly men. Several previous observational studies have reported a strong protective effect of TRT on all-cause mortality among TRT-treated patients.[11,12,34,47] However, they also found a strong protective effect on vascular outcomes, at least partly due to methodologic shortcomings.

Our study is notable for specifically evaluating the cardiovascular and cerebrovascular safety of TRT among men with low testosterone levels in the context of aging. Given the recent trends in which these medications are prescribed in the absence of underlying disease, our findings are therefore generalizable to a significant number of aging, but otherwise healthy men who may be considering treatment. Our analyses were also designed to circumvent the biases that may have influenced previous findings. Mainly, a time-varying TRT exposure definition was used to eliminate the potential for immortal time bias, and we further estimated the rate of events as a function of duration of TRT use. Despite these strengths, several limitations to our study must also be considered. First, while patients with testicular and hypogonadotropic disease were excluded, our cohort may still include a mix of patients with low testosterone levels due to other etiologies that may cause functional hypogonadism, including chronic opioid or glucocorticoid use, systemic illness, and obesity.[48] However, this heterogeneity reflects the prescribing patterns that have been observed in several countries, and our results are still informative with respect to the safety of TRT in this population. Second, in defining hypogonadism using laboratory test values, we were not able to account for known diurnal fluctuations in endogenous testosterone levels. Nevertheless, we assume that clinicians are adherent to local guidelines for testosterone testing, which recommend blood sampling and testosterone testing in the mornings only and during a fasting state.[48] Third, our definition of TRT exposure relied on prescriptions issued by general practitioners, and we were not able to determine patients' adherence to their prescribed treatment. However, given the consistency of our results using a variety of exposure definitions, we expect the impact of any exposure misclassification to have been minimal. Fourth, in the stratified analyses, our study was underpowered to draw a firm conclusion on a potential effect modification by age or prior history of cardiovascular disease. Thus, these prespecified secondary analyses should be interpreted with caution. In addition, it was only possible to examine the risk with all-cause mortality as we did not have information on death from cardiovascular causes. Finally, although our analyses accounted for numerous potential confounders, including lifestyle habits and time-varying confounders, residual confounding is possible given the observational nature of the study.

Our findings suggest that TRT may be associated with an increased risk of ischemic stroke/transient ischemic attack myocardial infarction among aging men with low testosterone levels, although the overall risk difference was low. Patients may be especially susceptible in the first 2 years after treatment initiation. Further large and methodologically sound observational studies should be conducted to reaffirm these results. Until such a time, the potential harms of TRT should be critically weighed against its perceived and expected benefits, and caution is warranted when prescribing these medications to aging but otherwise healthy men.

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SUPPLEMENTARY DATA

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