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Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

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Aims There is a significant uncertainty regarding the effect of testosterone replacement therapy (TRT) on cardiovascular (CV) outcomes including myocardial infarction (MI) and stroke. The aim of this study was to examine the relationship between normalization of total testosterone (TT) after TRT and CV events as well as all-cause mortality in patients without previous history of MI and stroke.

Methods and results We retrospectively examined 83 010 male veterans with documented low TT levels. The subjects were categorized into (Gp1: TRT with resulting normalization of TT levels), (Gp2: TRT without normalization of TT levels) and (Gp3: Did not receive TRT). By utilizing propensity score-weighted Cox proportional hazard models, the association of TRT with all-cause mortality, MI, stroke, and a composite endpoint was compared between these groups. The all-cause mortality [hazard ratio (HR): 0.44, confidence interval (CI) 0.42–0.46], risk of MI (HR: 0.76, CI 0.63–0.93), and stroke (HR: 0.64, CI 0.43–0.96) were significantly lower in Gp1 ($n = 43\,931$, median age = 66 years, mean follow-up = 6.2 years) vs. Gp3 ($n = 13\,378$, median age = 66 years, mean follow-up = 4.7 years) in propensity-matched cohort. Similarly, the all-cause mortality (HR: 0.53, CI 0.50–0.55), risk of MI (HR: 0.82, CI 0.71–0.95), and stroke (HR: 0.70, CI 0.51–0.96) were significantly lower in Gp1 vs. Gp2 ($n = 25\,701$, median age = 66 years, mean follow-up = 4.6 years). There was no difference in MI or stroke risk between Gp2 and Gp3.

Conclusion In this large observational cohort with extended follow-up, normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.

Keywords Testosterone replacement therapy • Myocardial infarction • Stroke

Introduction

Professional guidelines recommend testosterone replacement therapy (TRT) in patients with signs and symptoms of hypogonadism and documented evidence of low testosterone (T) levels.[1] The diagnosis of late-onset hypogonadism is on the rise with estimates that nearly 2.4 million men aged 40–69 suffer from hypogonadism in the USA.[2] Even though late-onset hypogonadism is not a universally accepted concept, and FDA has advised against T supplementation in men on the basis of age alone. However, in the last decade there has been a nearly 400% increase in the number of TRT prescriptions creating a billion dollar market.[3] With such widespread and ever increasing use of TRT, there has been growing concern regarding its effect on mortality and cardiovascular (CV) outcomes.

Recent retrospective studies, multiple meta-analyses, and a few small prospective studies have presented conflicting results and

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contributed to this uncertainty.[4–14] Observational studies suggested that low serum T level is associated with increased CV events.[4,15,16] Clinical trials examining TRT have been relatively small, and these trials were underpowered to provide conclusive evidence related to CV events.[9] For instance, a small prospective study in frail elderly men showed an increased incidence of CV events with TRT and was stopped early.[10] Two separate retrospective studies of men in the Veterans Affairs (VA) Health System using two different databases reported opposite effects of TRT on all-cause mortality.[11,14] In two very recent studies, Vigen *et al.*[11] using a VA database and Finkle *et al.*[12] using a healthcare database reported that men receiving TRT had an increased risk of myocardial infarction (MI). It is important to note that in many of these studies repeat measurements to document normalization of T levels after TRT were lacking. On the heels of these recently published data, the FDA issued a drug safety alert related to TRT (http://www.fda.gov/Drugs/DrugSafety/ucm383904.htm).

In light of these conflicting results and uncertainty concerning the safety of TRT, we have conducted a large retrospective study with long-term follow-up to address this knowledge gap. The objective of our study was to examine the association between TRT with documented normalization of total testosterone (TT) levels and all-cause mortality and adverse CV events defined by MI and stroke.

Methods

This is a retrospective cohort study of male veterans who received their medical care at the Veterans Health Administration (VHA) between December 1999 and May 2014. The data of study patients were retrieved from VHA Veterans Administrations Corporate Data Warehouse (CDW) through the Veterans Administrations Informatics and Computing Infrastructure (VINCI) [http://www.hsrd.research.va.gov/for_researchers/vinci/default.cfm (cited 21 June 2014)]. The study complies with the Declaration of Helsinki, and the Institutional Review Board of Kansas City Veterans Affairs Medical Center, MO, USA, approved the study. Additional details are provided in the Supplementary material online, *Appendix*.

Study design

This study was designed to examine the effect of TRT on CV outcomes by comparing the incidences of MI, stroke, and all-cause mortality among different sub-populations of treated and untreated patients. All patients' CV events and co-existing conditions were based on the International Classification of Diseases 9th Revision (ICD-9) codes. All of the study patients had TT levels checked at least on two separate occasions as recommended by guideline.[1]

Ascertainment of testosterone replacement therapy exposure

Use of TRT was ascertained from the medication prescription of patient medical records. For this study, patients who received any form of TRT (injection, gel or patch) were considered as treated.

Determination of total testosterone level

Low TT was determined to be present when TT level was less than the lower limit of normal laboratory reference range (NLRR) reported for that particular test result. This method was adopted to include results from a large number of laboratories in the entire VA Health System over a period of 14 plus years that used different test assays and had different reference ranges and reporting units. Data from position statement of Endocrine Society and several other sources suggest that testosterone levels can vary significantly between different laboratories, even when they use same commercial kits. Moreover, because of assay ambiguities and biological variations, no single cut-off T value can clearly distinguish between hypogonadism and eugonadism[17,18] There is also a lack of standardization when it comes to T levels and other tests using the stoichiometric measurements.[19,20] Hence, we classified each test result as low or normal based on its respective laboratory reference range reported. This approach permitted inclusion of testosterone values obtained using different assay methods and minimized the investigator bias likely introduced by an arbitrary cut-off value.

Outcome measures

Primary outcome measures were (i) the incidence of MI (ICD-9 410.x0 and 410.x1), (ii) the incidence of ischaemic stroke [ICD-9 433.x1, 434 (excluding 434.x0), or 436], and (iii) the all-cause mortality determined using dates of death in CDW data augmented with vital status files.

Additional details are provided in the Supplementary material online, *Appendix*.

Study population

Figure 1 presents the patient selection process.

Inclusion criteria

We included patients whose first tested TT level was lower than the respective laboratory NLRR.

Exclusion criteria

We excluded (i) females, (ii) those who received TRT before the first available low TT, (iii) those who had MI or ischaemic stroke before the first day of study, and (iv) those who on repeat testing had normal TT level before any treatment was started.

Eligible study patients were classified into three groups: Gp1: TRT with resulting normalization of TT levels (normalized-TRT); Gp2: TRT without normalization of TT levels (non-normalized-TRT); and Gp3: Did not receive TRT (no-TRT). Additional details are provided in the Supplementary material online, *Appendix*.

Statistical analysis

Continuous variables were reported as means and standard deviation (SD), categorical variables as percentages. Chi square test and Student's *t*-test were used to compare normally distributed baseline characteristics of patients. Non-parametric tests were used for non-normally distributed variables. We performed univariate and multivariable Cox proportional hazard regression analyses to assess the differences between groups. Furthermore, propensity scores were used to correct for potential systematic differences between treated and untreated patients. Each study patient's propensity scores for receiving the TRT were computed and adjusted for the covariates in a logistic regression analysis. The covariates included were age, body mass index (BMI), hypertension (HTN), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea (OSA), congestive heart failure (CHF), peripheral vascular disease (PVD), coronary artery disease (CAD), low density lipoprotein (LDL), use of aspirin, beta-blockers, and statins. All individuals with missing data on these matching covariates were excluded from the analysis. For robust analysis of our data, we utilized propensity score-weighted, stabilized inverse probability of treatment weights (IPTW); this allowed us to keep all patients in the study while using the propensity scores to achieve balance between each pair of subgroups we studied.[21–23]

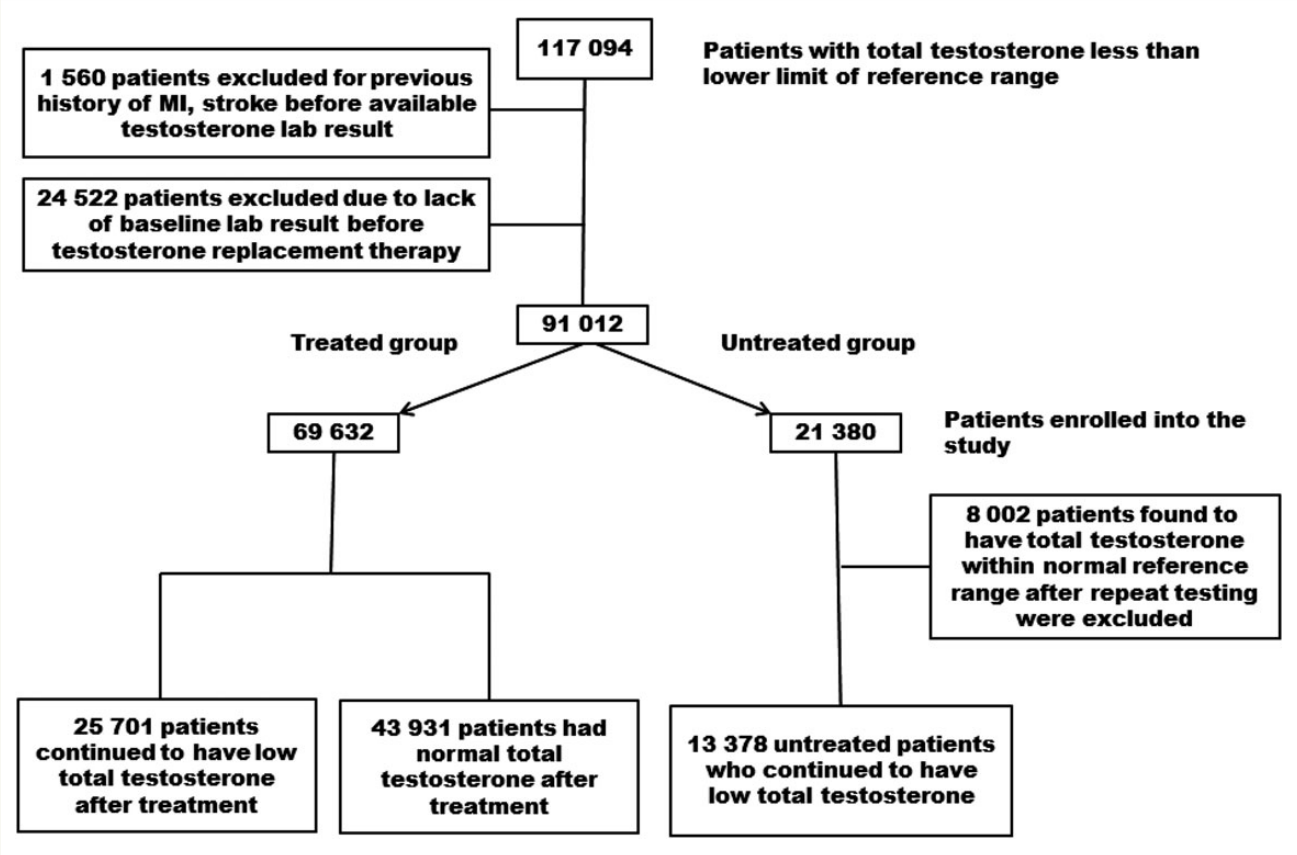

Figure 1 Methodology and patients selection process.

We also applied the stabilized IPTW to obtain Kaplan–Meier (KM) survival curves and to compare event-free survival time between the groups, along with log-rank *P*-value. SAS 9.4 was used for statistical analyses while Stata 12 was used to plot KM curves with TRT as a time-varying exposure variable. The study hypotheses were tested at two-sided level of significance with a *P*-value of <0.05. The use of IPTW effectively controlled for the imbalances in the groups as shown by the *P*-values (*Table 1*). Further details regarding how IPTW model was utilized in our study are described in the Supplementary material online, *Appendix*. Supplementary material online, *Figures S5–S7*, *Appendix* show how variations in low and high propensity scores in the unmatched pairs of cohorts were controlled for by IPTW.

Results

Cohort description

As shown in *Figure 1*, the initial cohort consisted of 117 094 patients with low TT. One thousand five hundred and sixty patients were excluded as they had a MI or stroke prior to the assessment of TT levels. These individuals were excluded because our study was focused on incident events. We then excluded 24 522 patients whose pretreatment baseline TT levels could not be ascertained. The remaining 91 012 patients were included in the study and categorized into those who received TRT at any time after they were determined to have low testosterone (81.5%) and those who did not receive TRT (18.5%). Testosterone replacement therapy achieved normalization of TT levels in 43 931 (63.1%) patients while the rest of this group continued to have low TT. Mean duration of treatment for normalized-TRT group was 3.0 ± 2.7 years and for non-normalized group was 1.5 ± 1.9 years.

In the untreated cohort, we identified certain individuals whose TT levels normalized at repeat testing ($n = 8002$). Though there was no record of treatment for these people, we could not rule out the possibility of non-VA prescriptions which could have been responsible for this finding. To prevent misclassification bias, individuals with these spuriously normalized TT levels were excluded leaving an *N* of 83 010. The percentage of people showing normal TT levels on repeat testing was around 30%; this number is consistent with the findings from population-based studies in which 1/3 of subjects showed normal TT levels on repeat testing.[24]

Baseline characteristics of the patients

Table 1 presents the baseline characteristics of the three groups. By means of stabilized IPTW, while performing Cox proportional hazard regression analyses, we controlled for discrepancies related to age, BMI, HTN, DM, COPD, OSA, CHF, PVD, CAD, LDL, use of aspirin, beta-blockers, and statins in the study groups by ensuring the cohorts were well matched ($P > 0.05$).

Table 1 Baseline characteristics of all study subjects

	Unmatched cohort			Propensity-matched cohort (stabilized IPTW)		
	Normalized treated vs. untreated					
	Normalized treated ***N*** **= 43 931**	**Untreated** ***N*** **= 13 378**	***P*-value**	**Normalized treated** ***N*** **= 40 852**	**Untreated** ***N*** **= 11 957**	***P*-value**
Age ≥ 50 years, *n* (%)	38 968 (89.4)	11 998 (90.3)	0.0055	36 641 (89.7)	10 716 (89.6)	0.8229
Age, median (Years)	66.0	67.0		66.0	67.0	
Body mass index ≥ 30 kg/m^2	28 670 (65.8)	8117 (63.7)	<0.0001	26 854 (65.7)	7871 (65.8)	0.8527
Body mass index, kg/m^2, mean (SD)	33.0 (6.6)	32.8 (6.9)		33.0 (6.6)	33.0 (6.8)	
Follow-up time (years), mean (SD)	6.2 (3.3)	4.7 (3.1)		6.0 (3.1)	4.6 (2.9)	
Hypertension, *n* (%)	7465 (17.0)	2342 (17.5)	0.1671	7251 (17.8)	2128 (17.8)	0.9118
Diabetes mellitus, *n* (%)	13 318 (30.3)	4228 (31.6)	0.0046	12 826 (31.4)	3762 (31.5)	0.8983
Chronic obstructive pulmonary disease, *n* (%)	528 (1.2)	215 (1.6)	0.0003	546 (1.3)	161 (1.3)	0.9676
Obstructive sleep apnoea, *n* (%)	801 (1.8)	279 (2.1)	0.0509	814 (2.0)	240 (2.0)	0.9428
Congestive heart failure, *n* (%)	713 (1.6)	353 (2.6)	<0.0001	779 (1.9)	228 (1.9)	0.9846
Peripheral vascular disease, *n* (%)	357 (0.8)	165 (1.2)	<0.0001	379 (0.9)	111 (0.9)	0.9759
Coronary artery disease	2141 (4.9)	738 (5.5)	0.0029	2146 (5.3)	629 (5.3)	0.9804
Depression, *n* (%)	3590 (8.2)	844 (6.3)	<0.0001	3284 (8.0)	957 (8.0)	0.8917
LDL > 100 mg/dL, *n* (%)	21 403 (51.6)	6085 (48.6)	<0.0001	20 779 (50.9)	6087 (50.9)	0.9297
Concomitant therapy with						
Antiplatelet agents (ASA), *n* (%)	12 410 (28.3)	3916 (29.3)	0.0217	11 904 (29.1)	3480 (29.1)	0.9451
B-blockers, *n* (%)	16 022 (36.5)	5041 (37.7)	0.0110	15 439 (37.8)	4515 (37.8)	0.9555
Statins, *n* (%)	25 260 (57.5)	7716 (57.7)	0.7161	24 334 (59.6)	7117 (59.5)	0.9237
	Normalized treated vs. non-normalized treated					
	Normalized treated ***N*** **= 43 931**	**Non-normalized treated** ***N*** **= 25 701**	***P*-value**	**Normalized treated** ***N*** **= 40 852**	**Non-normalized treated** ***N*** **= 23 953**	***P*-value**
Age ≥ 50 years, *n* (%)	38 968 (89.4)	22 692 (88.8)	0.0189	36 484 (89.3)	21 389 (89.3)	0.9945
Age, median (Years)	66.0	66.0		66.0	65.0	
Body mass index ≥ 30 kg/m^2	28 670 (65.8)	17 460 (69.0)	<0.0001	27 554 (67.4)	16 161 (67.5)	0.9327
Body mass index, kg/m^2, mean (SD)	33.0 (6.6)	33.6 (6.9)		33.2 (6.6)	33.4 (6.9)	
Follow-up time (years), mean (SD)	6.2 (3.3)	4.6 (3.1)		6.0 (3.1)	4.5 (3.0)	
Hypertension, *n* (%)	7465 (17.0)	5114 (19.9)	<0.0001	7655 (18.7)	4492 (18.8)	0.9502
Diabetes mellitus, *n* (%)	13 318 (30.3)	9233 (35.9)	<0.0001	13 512 (33.1)	7971 (33.1)	0.9967
Chronic obstructive pulmonary disease, *n* (%)	528 (1.2)	460 (1.8)	<0.0001	608 (1.5)	358 (1.5)	0.9509
Obstructive sleep apnoea, *n* (%)	801 (1.8)	712 (2.8)	<0.0001	936 (2.3)	549 (2.3)	0.9977
Congestive heart failure, *n* (%)	713 (1.6)	666 (2.6)	<0.0001	836 (2.1)	490 (2.0)	0.9892
Peripheral vascular disease, *n* (%)	357 (0.8)	291 (1.1)	<0.0001	386 (1.0)	227 (1.0)	0.9916

Continued

Table 1 *Continued*

	Unmatched cohort			Propensity-matched cohort (stabilized IPTW)		
	Normalized treated vs. untreated					
	Normalized treated N = 43 931	**Untreated N = 13 378**	***P*-value**	**Normalized treated N = 40 852**	**Untreated N = 11 957**	***P*-value**
Coronary artery disease	2141 (4.9)	1623 (6.3)	<0.0001	2304 (5.6)	1352 (5.6)	0.9742
Depression, *n* (%)	3590 (8.2)	2249 (8.8)	0.0078	3539 (8.7)	2079 (8.7)	0.9437
LDL > 100 mg/dL, *n* (%)	21 403 (51.6)	11 676 (47.8)	<0.0001	20 473 (50.1)	11 997 (50.1)	0.9621
Concomitant therapy with						
Antiplatelet agents (ASA), *n* (%)	12 410 (28.3)	7808 (30.4)	<0.0001	12 125 (29.7)	7111 (29.7)	0.9763
B-blockers, *n* (%)	16 022 (36.5)	10 532 (41.0)	<0.0001	15 947 (39.0)	9350 (39.0)	0.9884
Statins, *n* (%)	25 260 (57.5)	15 775 (61.4)	<0.0001	24 809 (60.7)	14 541 (60.7)	0.9675
	Non-normalized treated vs. untreated					
	Non-normalized treated N = 25 701	**Untreated N = 13 378**	***P*-value**	**Non-normalized treated N = 23 953**	**Untreated N = 11 957**	***P*-value**
Age ≥ 50 years, *n* (%)	22 692 (88.8)	11 998 (90.3)	<0.0001	21 391 (89.3)	10 677 (89.3)	0.9613
Age, median (Years)	66.0	67.0		66.0	67.0	
Body mass index ≥ 30 kg/m^2	17 460 (69.0)	8117 (63.7)	<0.0001	16 191 (67.6)	8086 (67.6)	0.9634
Body mass index, kg/m^2, mean (SD)	33.6 (6.9)	32.8 (6.9)		33.5 (6.9)	33.3 (6.9)	
Follow-up time (years), mean (SD)	4.6 (3.1)	4.7 (3.1)		4.5 (2.9)	4.5 (2.9)	
Hypertension, *n* (%)	5114 (19.9)	2342 (17.5)	<0.0001	4740 (19.8)	2370 (19.8)	0.9431
Diabetes mellitus, *n* (%)	9233 (35.9)	4228 (31.6)	<0.0001	8470 (35.4)	4231 (35.4)	0.9671
Chronic obstructive pulmonary disease, *n* (%)	460 (1.8)	215 (1.6)	0.1884	431 (1.8)	214 (1.8)	0.9718
Obstructive sleep apnoea, *n* (%)	712 (2.8)	279 (2.1)	<0.0001	645 (2.7)	323 (2.7)	0.9563
Congestive heart failure, *n* (%)	666 (2.6)	353 (2.6)	0.7806	644 (2.7)	324 (2.7)	0.9054
Peripheral vascular disease, *n* (%)	291 (1.1)	165 (1.2)	0.3771	288 (1.2)	145 (1.2)	0.9190
Coronary artery disease	1623 (6.3)	738 (5.5)	0.0017	1510 (6.3)	756 (6.3)	0.9504
Depression, *n* (%)	2249 (8.8)	844 (6.3)	<0.0001	1966 (8.2)	984 (8.2)	0.9342
LDL > 100 mg/dL, *n* (%)	11 676 (47.8)	6085 (48.6)	0.1484	11 489 (48.0)	5746 (48.1)	0.8731
Concomitant therapy with						
Antiplatelet agents (ASA), *n* (%)	7808 (30.4)	3916 (29.3)	0.0233	7359 (30.7)	3676 (30.8)	0.9649
B-blockers, *n* (%)	10 532 (41.0)	5041 (37.7)	<0.0001	9775 (40.8)	4875 (40.8)	0.9429
Statins, *n* (%)	15 775 (61.4)	7716 (57.7)	<0.0001	14 868 (62.1)	7419 (62.0)	0.9541

Relationship between testosterone replacement therapy and all-cause mortality

All-cause mortality in the three groups was as follows: normalized-TRT (Gp 1) (1654), non-normalized-TRT (Gp2) (3004), and no-TRT (Gp3) (3635) per 100 000 person-years. Normalized-TRT group had significantly fewer deaths than no-TRT (stabilized IPTW, hazard ratio, HR: 0.44, confidence interval, CI 0.42–0.46, $P < 0.0001$) and non-normalized-TRT (stabilized IPTW, HR: 0.53, CI 0.50–0.55, $P < 0.0001$) groups (*Table 2*). Mortality was also significantly lower in the non-normalized-TRT group compared with those in no-TRT group (stabilized IPTW, HR: 0.84, CI 0.80–0.89, $P < 0.0001$). The KM curves showed that the normalized-TRT group was associated with significantly increased all-cause mortality-free survival (log-rank, $P < 0.05$) compared with the non-normalized-TRT or no-TRT groups (*Figure 2*).

Relationship between testosterone replacement therapy and myocardial infarction

Table 2 presents result of the unadjusted and adjusted risk of MI in the study groups. Incidence of MI in the three groups was as follows: normalized-TRT group (189), non-normalized-TRT group (261), and no-TRT group (263) per 100 000 person-years. In the stabilized IPTW, normalized-TRT group showed lower risk of MI than non-normalized-TRT (HR: 0.82, CI 0.71–0.95, $P = 0.008$) and no-TRT (HR: 0.76, CI 0.63–0.93, $P = 0.005$) groups. However, non-normalized-TRT group was not different from no-TRT group (HR: 0.98, CI 0.80–1.19, $P = 0.811$). *Figure 3* shows a comparison of the probability of MI-free survival among the three groups. The KM curves show that normalized-TRT group was associated with significantly increased MI-free survival (log-rank, $P < 0.01$) compared with non-normalized-TRT and no-TRT groups. We performed additional analysis for MI-free survival after truncating the follow-up beyond 10 years. Although we lost a significant proportion of the study population, the findings remained fairly consistent after these analyses. See results in Supplementary material online, *Table S5* and *Figure S8*, Appendix.

Relationship between testosterone replacement therapy and ischaemic stroke

The incidence of ischaemic stroke was as follows: normalized-TRT group (43), non-normalized-TRT group (57), and no-TRT group (59) per 100 000 person-years. Stabilized IPTW showed that normalized-TRT group had significantly lower stroke events compared with non-normalized-TRT (HR: 0.70, CI 0.51–0.96, $P = 0.028$) and no-TRT (HR: 0.64, CI 0.43–0.96, $P = 0.031$) groups (*Table 2*). There was no difference in the risk of stroke between non-normalized-TRT group and no-TRT group. Overall, there was a protective effect against stroke in normalized-TRT group, as suggested by KM curves in Supplementary material online, *Figure S4, Appendix*.

Discussion

In this study of men with low TT levels and without prior MI or stroke, normalization of TT levels using TRT is associated with lower all-cause mortality, fewer MIs, and ischaemic strokes. This

Table 2 Unadjusted and adjusted hazard ratios for all-cause mortality, MI, and stroke

Model	All-cause mortality			Myocardial infarction			Stroke		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Comparing normalized treated vs. untreated (ref = untreated)									
Univariate $N = 43\,931$ vs. 13 378	0.40	0.39–0.43	<0.001	0.70	0.59–0.83	<0.001	0.57	0.40–0.82	0.002
Propensity matched (stabilized inverse probability of treatment weights) $N = 40\,852$ vs. 11 957	0.44	0.42–0.46	<0.001	0.76	0.63–0.93	0.005	0.64	0.43–0.96	0.031
Comparing normalized treated vs. non-normalized treated (ref = non-normalized treated)									
Univariate $N = 43\,931$ vs. 25 701	0.49	0.47–0.51	<0.001	0.74	0.64–0.85	<0.001	0.64	0.48–0.87	0.004
Propensity matched (stabilized inverse probability of treatment weights) $N = 40\,852$ vs. 23 953	0.53	0.50–0.55	<0.001	0.82	0.71–0.95	0.008	0.70	0.51–0.96	0.028
Comparing non-normalized treated vs. untreated (ref = untreated)									
Univariate $N = 25\,701$ vs. 13 378	0.83	0.79–0.87	<0.001	0.95	0.79–1.15	0.599	0.90	0.61–1.34	0.610
Propensity matched (stabilized inverse probability of treatment weights) $N = 23\,953$ vs. 11 957	0.84	0.80–0.89	<0.001	0.98	0.80–1.19	0.811	0.94	0.61–1.44	0.675

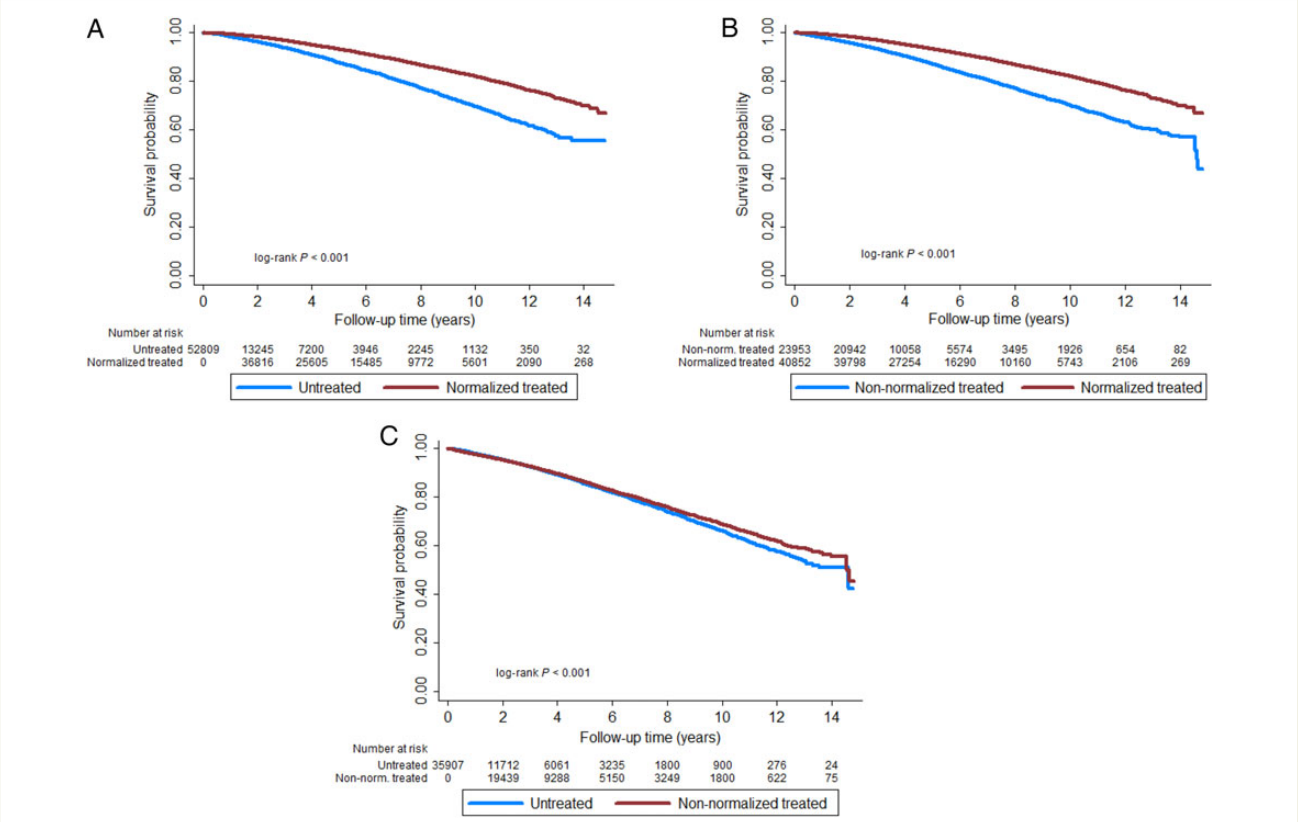

Figure 2 (*A*–*C*) Kaplan–Meier curve depicting the all-cause mortality among different propensity-matched study groups.

retrospective study describes the largest cohort of such patients and the longest follow-up for TRT to date. It is the first study to demonstrate that significant benefit is observed only if the dose is adequate to normalize the TT levels. Patients who failed to achieve the therapeutic range after TRT did not see a reduction in MI or stroke and had significantly less benefit on mortality. We selected patients without any previous history of MI or stroke prior to initiation of TRT to reduce bias related to CV outcomes. Further, we employed stabilized IPTW to decrease confounders by balancing measurable covariates between the groups. We modelled TRT as a time-varying covariate to account for the interval contributed by the treated individuals between enrollment (first low TT laboratory results) and the onset of TRT. We attempted to overcome the potential limitation of inadequate treatment by using follow-up TT levels as a marker of adequacy of dosing and compliance. We believe that our design criteria permit confidence in interpretation.

Several recent retrospective studies have investigated the association of TRT with CV outcomes. Vigen *et al.*[11] utilized the VA Clinical Assessment Reporting and Tracking (CART-CL) database that collects data from VA cardiac catheterization laboratories.[25] Their study enrolled patients who had cardiac catheterization done between 2005 and 2011 and also had low TT. The authors compared those who received TRT with those who did not. In that population, TRT was associated with significantly higher adverse events (MI, strokes, and death; HR: 1.29, 95% CI 1.05–1.58, $P = 0.02$). Our study differs from this study in several important ways. We included all patients who had their TT level checked, and we divided them into two groups: Gp1, patients who showed a documented appropriate rise in testosterone level post-TRT and Gp2, patients who did not achieve an appropriate rise. In comparison, Vigen *et al.* only included hypogonadal men who had undergone coronary angiography. This inclusion criterion may have introduced selection bias towards inclusion of a high CV-risk population. In this study, nearly 40% of the cohort had no repeat TT levels checked. Additionally, on the basis of the mean TT levels reported in the study by Vigen *et al.*, a number of patients likely did not achieve normalization of TT levels following TRT and, thus, may have reflected a subsequent risk of non-normalized hypogonadal men rather than a cohort with normalized TT level after TRT. Our study population was relatively healthier with lower average age (~64.2 years). Furthermore, we assessed hard end points (MI, stroke, and all-cause mortality).

The Testosterone in Older Men (TOM) trial[10] was a prospective, randomized placebo controlled study that was designed to determine the effects of TRT on lower extremity strength and physical function in older men with limitations in mobility and low serum levels of TT or free T. This trial was stopped prematurely at 6 months because of increased CV-related events in the TRT group. This trial had a small sample size (209 men), higher than average prevalence of chronic diseases (DM, HTN, and dyslipidaemia) in the cohort, and advanced age (mean age ~74 years); the adverse CV events were diverse and some were of variable clinical importance such as peripheral oedema, ectopy on ECG, and elevated BP. An additional

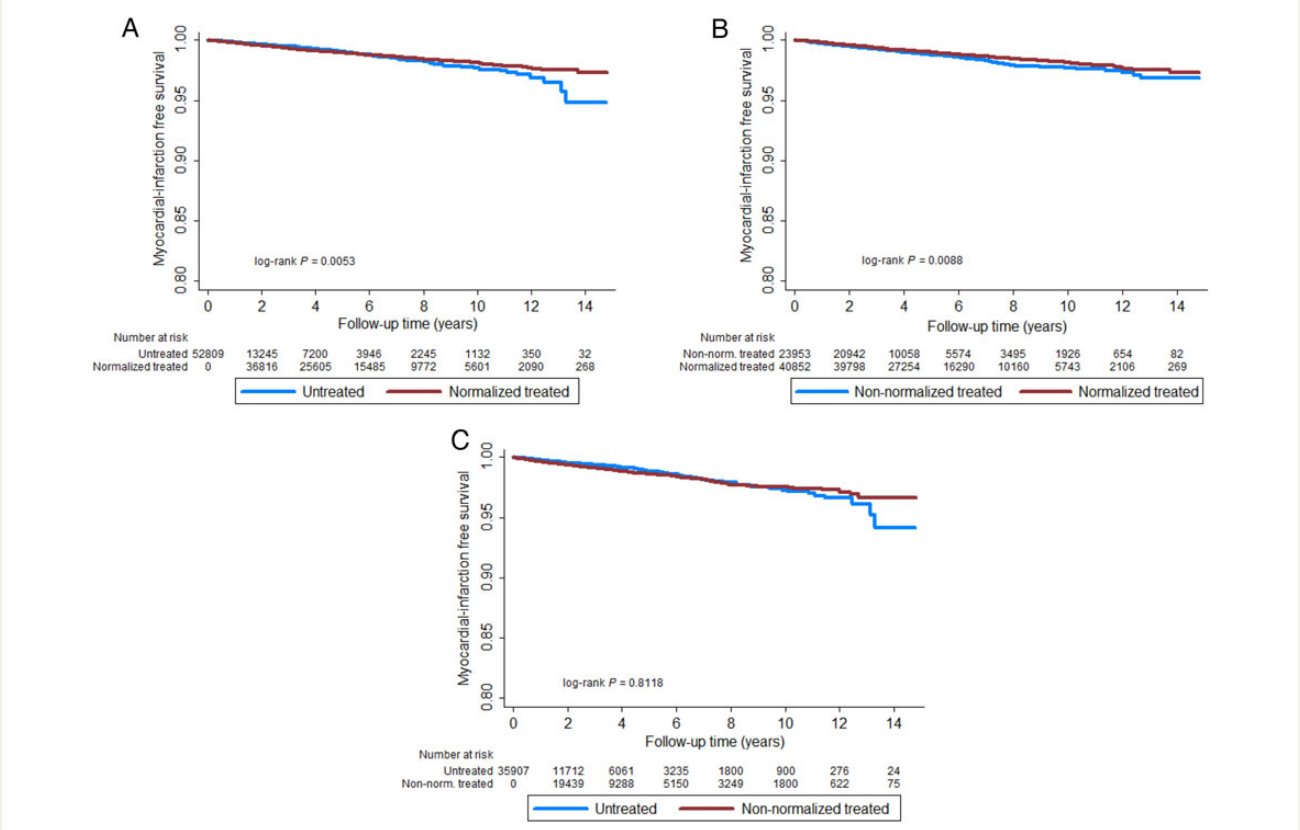

Figure 3 (*A*–*C*) Kaplan–Meier curve depicting the myocardial infarction-free survival among different propensity-matched study groups.

point worth noting was that early termination of the TOM trial may have contributed to an overestimation of the differences ascribed to treatment. In fact, some previous similar trials did not show an increased risk of adverse CV events with TRT therapy.[9,26]

A recent study by Finkle *et al.*[12] reported the risk of non-fatal MI in 90 days following a T prescription and compared it with the MI risk in the year preceding the prescription. They found that in older men (≥75 years) and in younger men with pre-existing heart disease, the risk of CV events was higher following a T prescription. However, this study did not take into account T levels. Thus, it is unclear how many people were adequately treated. Testosterone replacement therapy usually is a long-term therapy. These investigators limited the follow-up to 3 months of therapy. It is unknown whether this short duration of follow-up was sufficient to capture the outcomes of interest.

Our results do concur with a previous VA study. Shores *et al.*[14] analysed data from seven VA medical centers. They found that TRT was associated with a significant decrease in all-cause mortality (HR: 0.61, CI 95%, $P < 0.0001$). While supporting the results of Shores *et al.*, our study adds significantly to its conclusions both due to much larger sample size and also by more accurately identifying those who actually received and responded to the TRT. Shores *et al.* obtained data from the VA pharmacy records on T prescriptions, and those who received prescription were classified as treated. However, information regarding post-treatment TT level was not available in this study. Our study utilized post-TRT normalization in TT levels as a surrogate for administration of adequate therapy.

While our data found that normalization of TT levels after TRT was beneficial against CV risk and all-cause mortality, the mechanisms for these effects remain speculative. It can be postulated that the beneficial effect of normal T levels on adipose tissue, insulin sensitivity, and lipid profiles or by its anti-inflammatory and anticoagulant properties, as reported by other investigators, might have contributed to our findings.[27–29] However, there are other potential mechanisms such as sodium retention, CHF, increased platelet aggregation, or adverse changes in HDL through which T may increase the CV risks.[6] Therefore, additional studies will be needed to appropriately identify the mechanisms responsible for the outcomes noted in our study.

Finally, off-label use of TRT remains a concern. Recent FDA analyses suggest that currently only half of the men on TRT had been diagnosed with hypogonadism.[30] Furthermore, 25% of users did not have their T concentrations tested prior to initiating therapy, and 21% of those prescribed TRT did not have their levels tested at any time during treatment. Recently, a second advisory from the FDA posted caution about using testosterone products for low T due to ageing and requires labelling change to inform of possible increased risk of heart attack and stroke with use.[31] However, two very recent meta-analyses suggested a lack of convincing evidence posed by TRT.[32,33] Therefore, for now, to maximize the benefits of TRT and to mitigate potential risks, there is a need

for guideline-directed TRT with continuous active surveillance for potential risk in various cohorts of patients.

Study limitations

This was an observational study. Thus, unmeasured confounding or hidden bias might be present. A significant limitation of retrospective studies on TRT has been the inability to fully ascertain whether patients in the treatment arm actually took the medications in an adequate dose. This current study mostly overcomes this limitation by assessing follow-up TT levels. Normalization of follow-up TT levels is in our judgment a reliable surrogate for adequacy of dosing and compliance. Additionally, we could not ascertain the time of the day when the specimens for TT levels were drawn. Blood samples are usually collected during morning hours in the VA healthcare system. If some patients had their blood drawn after the morning hours, their levels would be underestimated. Furthermore, entry criteria and outcomes were determined using ICD-9 codes, and the VA cohort ICD-9 codes have been shown to be valid in determining outcomes.[11]

Another limitation of our study is that there was no randomization. Also our database does not have all the clinical data regarding indications for initiating TRT and not initiating TRT. Therefore, we cannot rule out the possibility that TRT may have been offered by a physician to healthier subjects and not to men who were less well. In our study, data regarding clinical response to TRT were also not available. Similarly, the available data do not permit us to ascertain the quality of care and/or poor compliance as reason(s) for persistent low testosterone levels observed in some individuals.

Despite the limitations associated with a retrospective study, our study has the advantages of having a large subject population with extensive follow-up. Our findings show that effective TRT is associated with lower rates of CV events in men without previous history of MI or stroke, in whom low TT levels are documented and effective TRT is provided. Safety and outcome of TRT in other populations remain to be determined.

Conclusion

Results from our present study suggest that in men without a history of previous MI or stroke who have low TT levels, TRT might be associated with decreased risks of MI, ischaemic stroke, and all-cause mortality in long-term follow-up. Our study also highlights that TRT should aim for doses resulting in normalization of TT level as this was shown to be associated with reduction in adverse CV events. In the future, adequately powered, prospective, well-designed trials with a long-term follow-up will be needed to reach a conclusive agreement regarding the effect of TRT on CV risk.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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