Relation of Testosterone Normalization to Mortality and Myocardial Infarction in Men With Previous Myocardial Infarction

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The effect of normalization of serum testosterone levels with testosterone replacement therapy (TRT) in patients with a history of myocardial infarction (MI) is unknown. The objective of this study was to determine the incidence of recurrent MI and all-cause mortality in subjects with a history of MI and low total testosterone (TT) with and without TRT. We retrospectively examined 1,470 men with documented low TT levels and previous MI, categorized into Gp1: TRT with normalization of TT levels (n = 755) Gp2: TRT without normalization of TT levels (n = 542), and Gp3: no TRT (n = 173). The association of TRT with all-cause mortality and recurrent MI was compared using propensity score-weighted Cox proportional hazard models. All-cause mortality was lower in Gp1 versus Gp2 (hazard ratio [HR] 0.76, confidence interval [CI] 0.64 to 0.90, p = 0.002), and Gp1 versus Gp3 (HR 0.76, CI 0.60 to 0.98, p = 0.031). There was no significant difference in the risk of death between Gp2 versus Gp3 (HR 0.97, CI 0.76 to 1.24, p = 0.81). Adjusted regression analyses showed no significant differences in the risk of recurrent MI between groups (Gp1 vs Gp3, HR 0.79, CI 0.12 to 5.27, p = 0.8; Gp1 vs Gp2 HR 1.10, CI 0.25 to 4.77, p = 0.90; Gp2 vs Gp3 HR 0.58, CI 0.08 to 4.06, p = 0.58). In conclusion, in a large observational cohort of male veterans with previous MI, normalization of TT levels with TRT was associated with decreased all-cause mortality compared with those with non-normalized TT levels and the untreated group. Furthermore, in this high-risk population, TRT was not associated with an increased risk of recurrent MI. Published by Elsevier Inc. (Am J Cardiol 2019;124:1171−1178)

Approximately 2.4 million men suffer from hypogonadism in the United States (US).[1] In the last decade, there has been a significant increase in the number of prescriptions for testosterone replacement therapy (TRT),[2] but the role of TRT and its effects on cardiovascular disease (CVD) remain controversial. Although previous studies evaluating TRT in men did not report adverse CV outcomes,[3−7] more recent studies have contradicted those findings.[8−10] Utilizing a large database of US military veterans, we previously found that normalization of total testosterone (TT) levels after TRT was associated with a significant reduction in all-cause mortality, myocardial infarction (MI), and stroke.[11] However, in that study, patients with a history of MI, a risk factor for recurrent adverse CV events in up to 40% of acute coronary syndrome patients,[12] were excluded. The impact of TRT on this high-risk population has not been reported previously. In the current study, we examined the effects of TRT in patients with a history of MI and documented low TT levels.

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Methods

We conducted a retrospective cohort study of male veterans who received medical care through the Veterans Health Administration (VHA) from December 1999 to May 2014. The VHA provides care to veterans at over 1,400 establishments across the United States, and each veteran is assigned a unique identifier in the Corporate Data Warehouse (CDW) database. Data were retrieved from the VHA CDW through the Veterans Administration Informatics and Computing Infrastructure.[13] The quality of data from these sources is well documented, and the data have been widely used by investigators for retrospective, longitudinal studies.[14] Data in the CDW are stored in a relational fashion and are definable by attributes such as the International Classification of Diseases, Ninth Revision (ICD-9) codes, Current Procedural Terminology codes, and other clinical measures, from both inpatient and outpatient encounters. The Veterans Administration Informatics and Computing Infrastructure provides a robust computing environment for researchers to analyze CDW data without moving sensitive health data off secure VA servers. The Institutional Review Board of the Veterans Affairs Medical Center in Kansas City, Missouri approved this study.

The current study examined the risk of recurrent MI among those who had a history of MI before their first low testosterone lab date. There was wide variability in the reporting units and reference ranges for testosterone test

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results over the extended follow-up period. The lack of standardization of TT levels using stoichiometric measurements has also been documented.[15,16] To eliminate the potential for disparities due to the use of multiple assays, we classified a test result as low or normal based on the respective normal laboratory reference range (NLRR) reported with the test result. TT levels less than the lower limit of the NLRR for a particular assay were categorized as low TT. This approach obviated the need for a single discrete cut-off value, because facilities used different TT assays, each with their own reference ranges and reporting units,[17,18] and enabled us to account for changes in the assays used over time within the same facility. We determined the use of TRT from both inpatient and outpatient prescription records. Patients were considered treated if they received any form of TRT (injection, gel, or patch); otherwise, they were considered as untreated. Treated patients were categorized as normalized or non-normalized depending on whether their TT levels improved to within the NLRR on treatment or remained persistently low.

The primary outcome measures were (1) recurrent MI (ICD-9 410.x0 and 410.x1) and (2) all-cause mortality. Mortality data were obtained from a combination of CDW files and Veteran's Health Administration Vital Status Files, the latter of which contains demographics, including dates of death obtained from multiple VA and non-VA data sources such as the Beneficiary Identification Records Locator Subsystem death file, the VA Medicare Vital Status File, and the Social Security Administration Death Master File.[19,20] Confounding variables that were adjusted for during the analysis were patient demographics, co-morbidities, including hypertension, congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, obstructive sleep apnea, low density lipoprotein levels, and peripheral vascular disease, and the use of medications, including aspirin, β blockers, and statins. Co-morbidities were defined using their respective ICD-9 codes.

We included patients whose first tested TT level was lower than the NLRR who also had a history of MI before the first documented low TT. We excluded (1) female patients, (2) those who received TRT before the first available low TT level, and (3) male patients without a history of MI. We used stabilized inverse probability of treatment weights (SIPTW) propensity score matching to ensure a robust analysis. SIPTW propensity score matching significantly corrects for the instability in estimated treatment weights that potentially results from the use of regular IPTW for individuals with a low probability of treatment.[21] This method allowed us to maximize the number of patients included in the study after matching, compared with traditional propensity score matching. We computed each subject's propensity score for receiving TRT and adjusted for the covariates in a logistic regression analysis. We computed the incidence of MI and all-cause mortality in each subgroup. Chi-squared test and the Student's *t* test were used to compare the normally distributed baseline characteristics of patients. Nonparametric tests were used for non-normally distributed variables. Univariate and multivariate Cox proportional hazard regression analyses were conducted to assess the differences between groups. We reported continuous variables as sample means and their standard deviations (SD), whereas categorical variables were reported as percentages. SAS Enterprise Guide 7.1 supported on SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) was used for statistical analyses, with TRT as a time-varying exposure variable. The study hypotheses were studied with two-tailed testing. A p value <0.05 was considered statistically significant.

Results

We identified 1,560 patients with low TT and a history of MI events before their first low TT lab (Figure 1). Of these, we excluded 90 patients who did not have complete data with respect to matching variables. The remaining

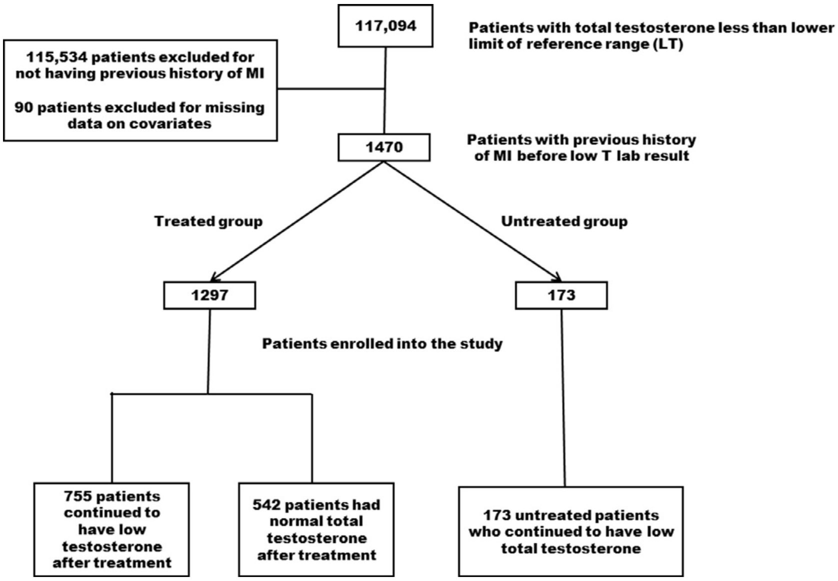

Figure 1. Methods and patient selection process.

Table 1
Baseline variables for the unmatched and SIPTW-matched cohorts of all patients in the study

Variable	Unmatched cohort			Propensity matched cohort (Stabilized- IPTW)		
	Normalized-treated vs untreated (ref = untreated)					
	Normalized treated (n = 755)	Untreated (n = 173)	p Value	Normalized treated (n = 755)	Untreated (n = 176)	p Value
Age ≥50 years	736 (97.5%)	172 (99.4%)	0.1133	739 (97.8%)	169 (96.2%)	0.2142
Age, median (years)	64.3	66.5		64.4	64.3	
Body mass index ≥30 kg/m^2	439 (58.2)	98 (56.7)	0.7189	437 (57.8)	104 (59.4)	0.7072
Body mass index kg/m^2, mean (SD)	31.6 (6.1)	31.5 (6.6)		31.5 (6.1)	31.9 (6.5)	
Follow-up time (years), mean (SD)	4.0 (3.4)	3.3 (3.1)		4.0 (3.4)	3.7 (3.6)	
Hypertension	630 (83.4%)	156 (90.2%)	0.0266	639 (84.7%)	144 (82.2%)	0.4214
Diabetes mellitus	323 (42.8%)	82 (47.4%)	0.2694	329 (43.6%)	73 (41.6%)	0.6355
Chronic obstructive pulmonary disease	48 (6.4%)	16 (9.3%)	0.1759	52 (6.9%)	12 (6.5%)	0.8735
Obstructive sleep apnea	81 (10.7%)	20 (11.6%)	0.7512	82 (10.9%)	18.3 (10.4%)	0.8675
Congestive heart failure	173 (22.9%)	49 (28.3%)	0.1325	181 (24.0%)	42 (23.9%)	0.9894
Peripheral vascular disease	69 (9.1%)	15 (8.7%)	0.8464	68 (9.0%)	15 (8.5%)	0.8295
Depression	217 (28.7%)	44 (25.4%)	0.3827	212 (28.1%)	47 (26.9%)	0.7535
LDL >100 mg/dl	239 (31.7%)	54 (31.2%)	0.9102	238 (31.5%)	52 (29.3%)	0.5737
Concomitant therapy with:						
Antiplatelet Agents (ASA)	677 (89.7%)	152 (87.9%)	0.4873	675 (89.4%)	158 (90.0%)	0.8047
B-blockers	712 (94.3%)	162 (93.6%)	0.7369	711 (94.2%)	167 (94.8%)	0.7616
Statins	719 (95.2%)	162 (93.6%)	0.3896	717 (95.0%)	168 (95.8%)	0.6700
	Normalized-treated vs non-normalized-treated (ref = non-normalized treated)					
	Normalized treated (n = 755)	Non-normalized-treated (n = 542)	p Value	Normalized treated (n = 755)	Non-normalized-treated (n = 542)	p Value
Age ≥50 years	736 (97.5%)	528 (97.4%)	0.9402	736 (97.5%)	528 (97.4%)	0.9770
Age, median (years)	64.3	64.5		64.3	64.5	
Body mass index ≥30 kg/m^2	439 (58.2)	335 (61.8)	0.1848	451 (59.7)	324 (59.7)	0.9987
Body mass index kg/m^2, mean (SD)	31.6 (6.1)	32.3 (6.1)		31.8 (6.2)	32.1 (6.1)	
Follow-up time (years), mean (SD)	4.0 (3.4)	3.4 (3.2)		4.0 (3.3)	3.4 (3.2)	
Hypertension	630 (83.4%)	456 (84.1%)	0.7401	632 (83.7%)	454 (83.7%)	0.9867
Diabetes mellitus	323 (42.8%)	267 (49.3%)	0.0208	343 (45.5%)	246 (45.5%)	0.9918
Chronic obstructive pulmonary disease	48 (6.4%)	52 (9.6%)	0.0312	59 (7.8%)	42 (7.7%)	0.9960
Obstructive sleep apnea	81 (10.7%)	68 (12.6%)	0.3113	86 (11.4%)	62 (11.4%)	0.9835
Congestive heart failure	173 (22.9%)	142 (26.2%)	0.1736	183 (24.3%)	131 (24.2%)	0.9788
Peripheral vascular disease	69 (9.1%)	52 (9.6%)	0.7811	70 (9.2%)	50 (9.2%)	0.9788
Depression	217 (28.7%)	164 (30.3%)	0.5542	222 (29.4%)	159 (29.3%)	0.9817
LDL >100 mg/dl	239 (31.7%)	172 (31.7%)	0.9760	239 (31.7%)	171 (31.6%)	0.9790
Concomitant therapy with:						
Antiplatelet Agents (ASA)	677 (89.7%)	491 (90.6%)	0.5844	680 (90.0%)	488 (90.0%)	0.9875
B-blockers	712 (94.3%)	510 (94.1%)	0.8738	712 (94.3%)	511 (94.3%)	0.9887
Statins	719 (95.2%)	521 (96.1%)	0.4387	722 (95.6%)	519 (95.7%)	0.9875
	Non-normalized-treated vs untreated (ref = untreated)					
	Non-normalized-treated (n = 542)	Untreated (n = 173)	p Value	Non-normalized-treated (n = 542)	Untreated (n = 174)	p Value
Age ≥50 years	528 (97.4%)	172 (99.4%)	0.1091	531 (97.9%)	169 (97.2%)	0.5960
Age, median (years)	64.5	66.5		64.8	64.3	
Body mass index ≥30 kg/m^2	335 (61.8)	98 (56.7)	0.2266	328 (60.4)	104 (59.9)	0.9043
Body mass index kg/m^2, mean (SD)	32.3 (6.1)	31.5 (6.6)		32.2 (6.1)	31.9 (6.6)	
Follow-up time (years), mean (SD)	3.4 (3.2)	3.3 (3.1)		3.4 (3.2)	3.6 (3.4)	
Hypertension	456 (84.1%)	156 (90.2%)	0.0488	463 (85.6%)	146 (84.1%)	0.6407
Diabetes mellitus	267 (49.3%)	82 (47.4%)	0.6695	264 (48.7%)	82 (47.4%)	0.7614
Chronic obstructive pulmonary disease	52 (9.6%)	16 (9.3%)	0.8927	52 (9.5%)	17 (9.5%)	0.9817
Obstructive sleep apnea	68 (12.6%)	20 (11.6%)	0.7312	67 (12.3%)	21 (11.9%)	0.8897
Congestive heart failure	142 (26.2%)	49 (28.3%)	0.5824	145 (26.8%)	47 (27.1%)	0.9415
Peripheral vascular disease	52 (9.6%)	15 (8.7%)	0.7167	51 (9.4%)	16 (9.4%)	0.9978
Depression	164 (30.3%)	44 (25.4%)	0.2238	158 (29.1%)	49 (28.2%)	0.8287
LDL >100 mg/dl	172 (31.7%)	54 (31.2%)	0.8980	171 (31.6%)	52 (29.9%)	0.6831

(*continued*)

Table 1 (***Continued***)

	Non-normalized-treated vs untreated (ref = untreated)					
	Non-normalized-treated (n = 542)	Untreated (n = 173)	p Value	Non-normalized-treated (n = 542)	Untreated (n = 174)	p Value
Concomitant therapy with:						
Antiplatelet Agents (ASA)	491 (90.6%)	152 (87.9%)	0.2990	487 (89.9%)	156 (89.7%)	0.9476
B-blockers	510 (94.1%)	162 (93.6%)	0.8268	509 (94.0%)	164 (94.2%)	0.9018
Statins	521 (96.1%)	162 (93.6%)	0.1689	518 (95.5%)	166 (95.7%)	0.9070

patients were categorized as follows: Gp1, TRT with normalization of TT levels (n = 755); Gp2, TRT without normalization of TT levels (n = 542); and Gp3, those who did not receive TRT at any time (n = 173).

Table 1 displays baseline variables for the unmatched and SIPTW-matched cohorts. Median ages at enrollment were 64.3 years, 64.5 years, and 66.5 years for Gp1, Gp2, and Gp3, respectively. The cohorts were predominantly obese with mean body mass index at enrollment being 31.6 kg/m^2 (SD 6.1), 32.3 kg/m^2 (SD 6.1), and 32.3 kg/m^2 (SD 6.1) in Gp1, Gp2, and Gp3, respectively. Mean follow-up time was longer in the normalized TRT group (Gp1, 4.0 years, SD 3.4) than the non-normalized TRT (Gp2, 3.4 years, SD 3.2), and the untreated (Gp3, 3.3 years, SD 3.1) groups. We adjusted for the differences in age, body mass index, and other baseline co-morbidities by means of SIPTW matching. Enhancing the yield and validity of Cox proportional hazard regression analyses, all groups were well matched (p >0.05) with regard to these covariates, as presented in Table 1.

Mortality rates among groups were as follows: normalized TRT (Gp1), 101 per 1,000 person-years; non-normalized TRT (Gp2), 137 per 1,000 person-years; and untreated (Gp3), 163 per 1,000 person-years. The risk of death from

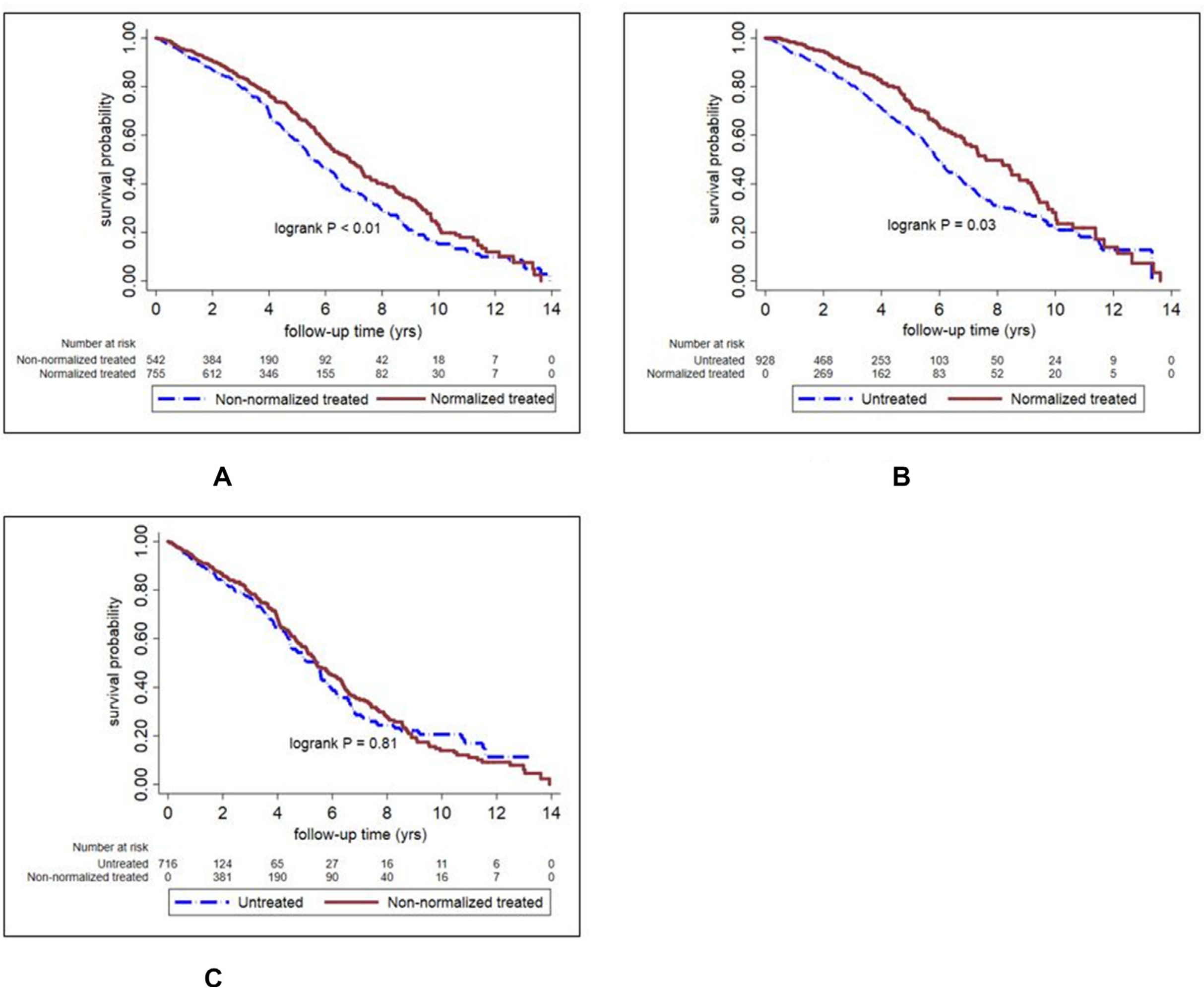

Figure 2. Kaplan-Meier curve comparing the all-cause-mortality in the non-normalized treated versus normalized treated group (*A*), untreated versus normalized treated groups (*B*), and untreated versus non-normalized treated groups (*C*).

any cause was significantly lower in Gp1 compared with Gp2 (HR 0.76, 95% CI 0.64 to 0.90, p = 0.002), and in Gp1 compared with Gp3 (HR 0.76, 95% CI 0.60 to 0.98, p = 0.031). There was no significant difference in the risk of all-cause mortality between Gp2 and Gp3 (HR 0.97, 95% CI 0.76 to 1.24, p = 0.81). Kaplan-Meier survival curves were constructed (Figure 2), which demonstrated that normalization of TRT (Gp1) was associated with significantly greater survival from all-cause death (log-rank p <0.05), compared with non-normalized TRT (Gp2) or untreated (Gp3) groups.

The incidence of recurrent MI in each group was as follows: normalized TRT (Gp1), 1,391 per 100,000 person-years; non-normalized TRT (Gp2), 1,628 per 100,000 person-years; untreated (Gp3), 1,402 per 100,000 person-years. Table 2 presents the results of the Cox proportional hazard regression analysis. There were no significant differences in the risks of recurrent MI between groups: Gp1 versus Gp3 (HR 0.79, 95% CI 0.12 to 5.27, p = 0.81); Gp1 versus Gp2 (HR 1.10, 95% CI 0.25 to 4.77, p = 0.90); Gp2 versus Gp3 (HR 0.58, 95% CI 0.08 to 4.06, p = 0.58). TRT did not appear to be significantly associated with an increased risk of recurrent MI. The Kaplan-Meier curves (Figure 3) additionally showed no difference in MI-free survival among the groups (log-rank p >0.05).

Discussion

In this study of hypogonadal patients with a history of MI there are several key findings. First, in this population, normalization of TT levels after TRT was associated with a significant decrease in all-cause mortality, compared with those who received TRT without normalization of TT levels and those not treated. Second, there was no statistically significant difference in all-cause mortality between the non-normalized TRT group (Gp2) and the untreated group (Gp3). Finally, there was no significant increase in the incidence of recurrent MI in subjects receiving TRT with subsequent complete or incomplete TT normalization.

Clinical trials examining the effects of TRT historically have been small and underpowered to provide conclusive evidence on the risk of adverse CV events.[22] Early trials found that TRT reduced symptoms in patients with chronic stable angina.[23,24] In one study, there were no significant difference in carotid intimal medial thickness or coronary artery calcium scores in over 3 years of follow-up, between patients receiving TRT or placebo.[25] In the largest observational study to date, our group previously found that normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke in patients without a history of MI or stroke.[11] A recent meta-analysis also found no significant association of TRT with adverse CV events.[26]

The first major trial describing adverse CV outcomes after TRT was the Testosterone in Older Men (TOM) trial,[8] a randomized controlled trial designed to determine the effects of TRT on lower extremity strength and physical function in older men with limited mobility over 6 months. Although the study was not powered to assess CV events, it reported a higher incidence of CV-related events in the treatment arm. These events were diverse and of variable clinical importance (e.g., peripheral edema, ectopy on electrocardiography). In an observational study by Vigen et al, examining data from VA cardiac catheterization laboratories, TRT was

Table 2
Unadjusted and adjusted hazard ratios for all-cause mortality and recurrent myocardial infarction

Comparing normalized-treated vs untreated (ref = untreated)						
Model	All-cause mortality			Myocardial infarction		
	HR	95% CI	p	HR	95% CI	p
Univariate n = 755 vs 173	0.568	0.450-0.717	<.0001	0.496	0.096-2.568	0.4031
Propensity Matched (Stabilized IPTW) n = 755 vs 176	0.764	0.598-0.976	0.0312	0.790	0.118-5.267	0.8073
Comparing normalized-treated vs non-normalized-treated (ref = non-normalized treated)						
Model	All-cause mortality			Myocardial infarction		
	HR	95% CI	p	HR	95% CI	p
Univariate n = 755 vs 542	0.722	0.611-0.854	0.0001	1.027	0.245-4.307	0.9710
Propensity matched (Stabilized IPTW) n = 755 vs 542	0.759	0.639-0.901	0.0017	1.099	0.253-4.764	0.9000
Comparing non-normalized-treated vs untreated (ref = untreated)						
Model	All-cause mortality			Myocardial infarction		
	HR	95% CI	p	HR	95% CI	p
Univariate n = 542 vs 173	0.808	0.636-1.025	0.0791	0.474	0.079-2.836	0.4133
Propensity Matched (Stabilized IPTW) n = 542 vs 174	0.970	0.757-1.243	0.8084	0.575	0.082-4.061	0.5794

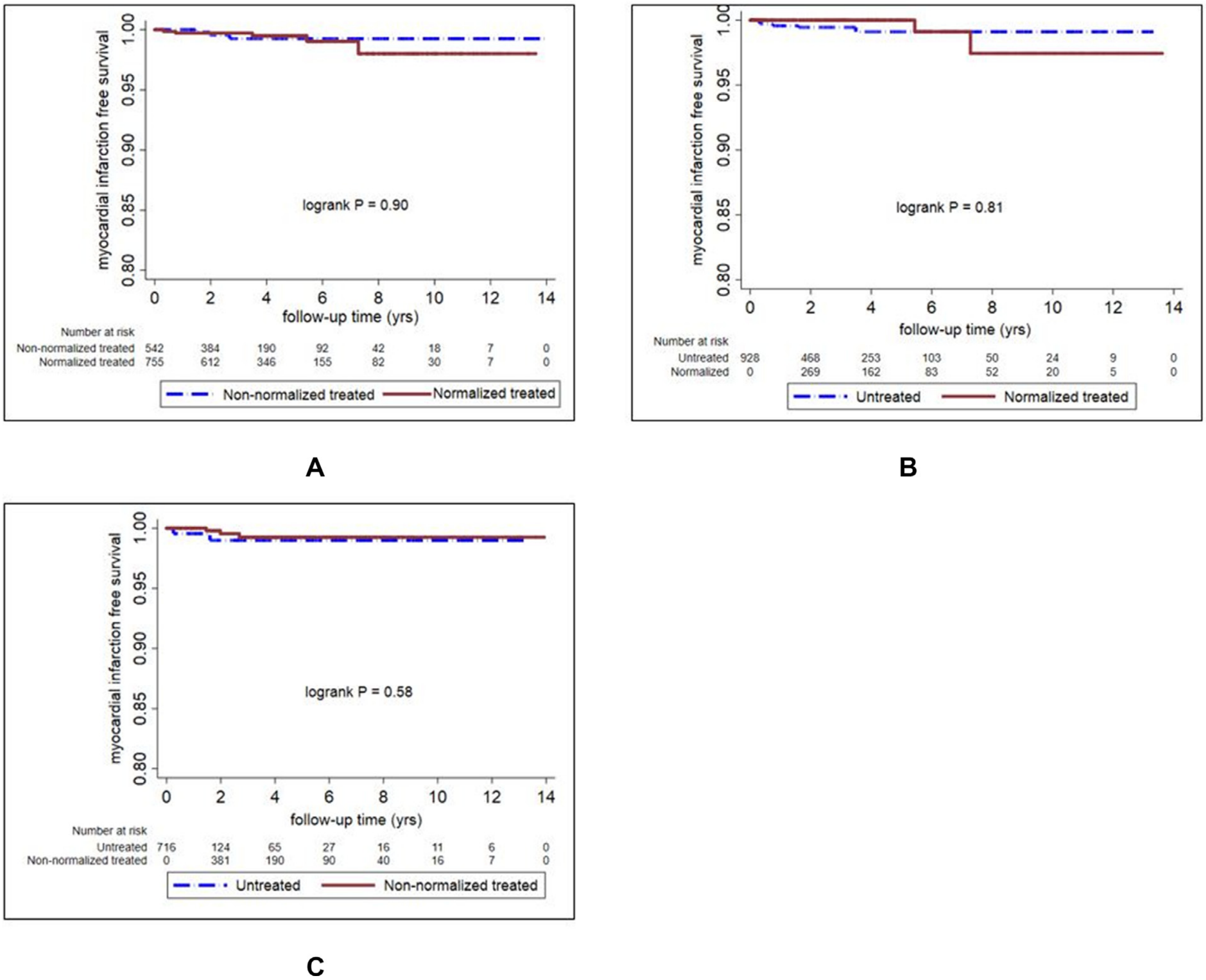

Figure 3. Kaplan-Meier curve comparing recurrent myocardial infarction in the non-normalized treated versus normalized treated group (*A*), untreated versus normalized treated groups (*B*), and untreated versus non-normalized treated groups (*C*).

significantly associated with a higher number of composite adverse events (MI, stroke, and death; HR 1.29, 95% CI 1.05 to 1.58, p = 0.02). In this study, 20% of the population had a history of MI,[9] and inclusion of men who underwent coronary angiography might itself have introduced selection bias, resulting in a higher CV risk population.[11,26] Recently, Budoff et al reported that TRT gel administration for 1 year was associated with a significant increase in coronary artery noncalcified plaque volume measured by coronary computed tomographic angiography,[27] but men with a history of MI or stroke within 3 months were excluded.

The present study examined the effect of TRT in patients with a higher CV risk than many previous studies, as all subjects had a history of MI. Despite the increased risk, the results were consistent with our previous findings in a male veteran population, excluding those with a history of stroke or MI, in which normalization of TT levels after TRT was also associated with decreased all-cause mortality compared with those with incomplete normalization.[11] In the current study, we found TRT with incomplete or complete TT normalization was not associated with an increase or decrease in recurrent MI. This finding differs from our previous results and is likely due to a lower CV risk in that population (no history of MI and stroke, and only 6% had coronary artery disease), as compared with the current study.[11]

The lack of reduction in MI after TRT in patients with previous MI suggests normalization of TT alone may not be sufficient to reduce MI events in this high-risk population. Given the multifactorial nature of atherosclerotic coronary artery disease and complex pathophysiology of acute coronary syndrome, a comprehensive risk factor reduction strategy is needed to reduce the risk of recurrent MI. Unlike the study of Vigen et al, in which 20% of the population had a history of MI,[9] our study examining an entirely post-MI cohort did not show an association between TRT and adverse CV outcomes. Based on the mean TT levels reported by Vigen et al, a number of patients likely did not achieve normalization of TT levels after TRT and may therefore have been at increased risk compared with a cohort with normalized TT levels after TRT. Although further study is needed to better define the appropriate role for TRT in patients with a history of CVD, in carefully selected hypogonadal patients there may be a role for TRT. Despite the controversies surrounding TRT,[8,9] current guidelines and scientific consensus statements indicate the totality of evidence favors a lack of adverse CV events due to TT normalization with TRT.[28−31] Our study fortifies this position with evidence regarding the effects of TRT in a high-risk population.

There were a number of limitations in the current study. Our study results are specific to the population studied and may not be generalized. Given its observational nature, residual confounding cannot be entirely ruled out. Inclusion criteria and outcomes were determined using ICD-9 and Current Procedural Terminology codes. CDW does not capture the reasons for initiating/withholding TRT, so we cannot rule out the possibility that TRT was preferentially offered to healthier subjects. In our study, data regarding clinical response to TRT were also not available. Similarly, we were unable to study quality of care and/or poor compliance as reason(s) for persistent low testosterone levels observed in some individuals.

In conclusion results from our study illustrate that in a high CV risk population with a history of MI, TRT with normalization of TT levels is associated with decreased all-cause mortality. Exposure to TRT, resulting in normalized or non-normalized TT levels, had no significant effect on recurrent MI compared with untreated subjects, suggesting the safety of TRT this population. These findings and our understanding of the CV effects of TRT will be further enhanced with adequately powered, prospective clinical trials featuring long-term follow-up.

Disclosures

None of the authors have a conflict of interest regarding the contents of the paper. Views expressed in this article are those of authors and do not necessarily reflect the position and policy of the Department of Veterans Affairs or the United States Government.

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