Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

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IMPORTANCE Rates of testosterone therapy are increasing and the effects of testosterone therapy on cardiovascular outcomes and mortality are unknown. A recent randomized clinical trial of testosterone therapy in men with a high prevalence of cardiovascular diseases was stopped prematurely due to adverse cardiovascular events raising concerns about testosterone therapy safety.

OBJECTIVES To assess the association between testosterone therapy and all-cause mortality, myocardial infarction (MI), or stroke among male veterans and to determine whether this association is modified by underlying coronary artery disease.

DESIGN, SETTING, AND PATIENTS A retrospective national cohort study of men with low testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011.

MAIN OUTCOMES AND MEASURES Primary outcome was a composite of all-cause mortality, MI, and ischemic stroke.

RESULTS Of the 8709 men with a total testosterone level lower than 300 ng/dL, 1223 patients started testosterone therapy after a median of 531 days following coronary angiography. Of the 1710 outcome events, 748 men died, 443 had MIs, and 519 had strokes. Of 7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Among 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. The absolute rate of events were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group, with an absolute risk difference of 5.8% (95% CI, −1.4% to 13.1%) at 3 years after coronary angiography. In Cox proportional hazards models adjusting for the presence of coronary artery disease, testosterone therapy use as a time-varying covariate was associated with increased risk of adverse outcomes (hazard ratio, 1.29; 95% CI, 1.04 to 1.58). There was no significant difference in the effect size of testosterone therapy among those with and without coronary artery disease (test for interaction, $P = .41$).

CONCLUSIONS AND RELEVANCE Among a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes. These findings may inform the discussion about the potential risks of testosterone therapy.

Editorial page 1805

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JAMA Patient Page 1872

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Rates of testosterone therapy prescription have increased markedly in the United States over the past decade. Annual prescriptions for testosterone increased by more than 5-fold from 2000[1] to 2011, reaching 5.3 million prescriptions and a market of $1.6 billion in 2011.[2,3] Professional society guidelines recommend testosterone therapy for patients with symptomatic testosterone deficiency.[4] In addition to improving sexual function[5-7] and bone mineral density[8,9] and increasing free-fat mass[8,9] and strength,[10] treatment with testosterone has been shown to improve lipid profiles[11-13] and insulin resistance[11,12] and increase the time to ST depression during stress testing.[14,15]

The effects of testosterone therapy on cardiovascular outcomes and mortality are unknown. Prior clinical studies of testosterone therapy have not detected adverse cardiac events, but these trials were generally focused on intermediate end points, of short duration, and not powered for clinical end points. A recent trial, the Testosterone in Older Men with Mobility Limitations (TOM) trial,[16] conducted in older frail men with a high prevalence of cardiovascular diseases was stopped prematurely due to increased cardiovascular events in the treatment group. The premature termination of the TOM trial and the limitations of the prior studies highlight uncertainty regarding the safety of testosterone therapy in older men with cardiovascular diseases.

CABG *coronary artery bypass graft*
CAD *coronary artery disease*
CT *computed tomography*
MI *myocardial infarction*
PCI *percutaneous intervention*
VA *Veterans Affairs*

To address this gap in knowledge, we evaluated the association between the use of testosterone therapy and all-cause mortality, myocardial infarction (MI), and stroke among male veterans and whether this association was modified by underlying coronary artery disease (CAD).

Methods

The VA Clinical Assessment Reporting and Tracking (CART) Program uses a customized software application that collects patient and procedural data at the point-of-care for all procedures performed in the 76 VA cardiac catheterization laboratories nationwide.[17,18] It is designed to simultaneously allow for data entry by clinicians during routine clinical workflow, integrate into the VA's electronic medical record system, and collect individual and aggregate data to support quality management and improvement initiatives for cardiovascular procedures. CART was initially implemented in 2005 and was actively used in all VA catheterization laboratories by 2009. The methods of its implementation have been previously described.[17] This study was approved by the Colorado Multiple Institutional Review Board.

Patient Population

This was a retrospective cohort study of all male veterans who underwent coronary angiography between 2005 and 2011 and who had a total testosterone level checked. Patients who started testosterone therapy prior to coronary angiography were excluded because we could not ascertain the effect of testosterone therapy treatment on underlying burden of coronary disease. Additionally, patients who started testosterone therapy prior to having a testosterone level checked in the VA were excluded because we did not know if the patient had low testosterone levels prior to treatment. Patients with missing coronary anatomy data and those who were prescribed testosterone therapy after an MI were excluded. Patients with a hematocrit of more than 50% and a prostate-specific antigen (PSA) level of 4.0 ng/mL or higher were excluded because these are contraindications to testosterone therapy per guidelines.[4] The final cohort was limited to patients who had a total testosterone level less than 300 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) because this is a generally agreed threshold for biochemical hypogonadism per the Endocrine Society Clinical Practice Guidelines.[4]

Covariates

Patient characteristics and presence of CAD were obtained via CART and VA administrative data.[18] Patient characteristics are entered into CART at the time of coronary angiography by physicians performing the procedure in the cardiac catheterization laboratory. Covariates not present in CART were obtained from VA administrative data, the majority of which were derived from Elixhauser codes. Total testosterone levels were obtained from VA laboratory files, and the level closest in timing to the procedure date was included in this analysis. Coronary artery disease was present if there was 20% or more stenosis in any epicardial vessel as recorded in CART by the physician performing the procedure. No evidence of CAD was defined as less than 20% stenosis in all epicardial vessels on angiography. These definitions were chosen based on standardized definitions of flow-limiting stenosis.[19,20]

Primary Exposure Variable

Patients were categorized as initiating testosterone therapy if they filled a prescription for testosterone gel, patch, or injections following coronary angiography based on pharmacy-dispensing data (VHA Decision Support System). Once initiated, a patient was assumed to have continued treatment until an outcome event occurred or the end of follow-up. Testosterone therapy is generally prescribed long-term with recommendations for assessment of response and adverse effects at 3 months following initiation and then annually thereafter.[4]

Outcome Variable

The primary end point was a combined end point of time to all-cause mortality or to hospitalization for MI or ischemic stroke. All-cause mortality was assessed via the VA vital status file. The file has 98.3% sensitivity and 97.6% exact agreement with the National Death Index.[21,22] Myocardial infarction and ischemic stroke were assessed via *International Classification of Diseases, Ninth Revision (ICD-9)* codes (410.x0 and 410.x1) and (433.x or 444.x), respectively, from VA inpatient treatment files. The last day of follow-up was January 23, 2012.

Statistical Methods

Because patients were not randomized to receive testosterone therapy, we used stabilized inverse probability of treatment weighting to adjust for any unmeasured confounders that may have affected when and if patients were prescribed testosterone therapy. Variables used to create these weights included demographic characteristics (age, race), comorbidities (prior MI, congestive heart failure, diabetes, renal failure, depression, posttraumatic stress disorder, hyperlipidemia, peripheral vascular disease, chronic pulmonary disease, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension, cerebrovascular disease, overweight, dialysis, ever smoker, alcohol, anemia, blood loss anemia, coagulation disorder, complicated diabetes, uncomplicated diabetes, drug abuse, fluid electrolyte disorder, human immunodeficiency syndrome or AIDS, hypothyroidism, liver disease, lymphoma, metastatic cancer, neurological disorder, paralysis, peptic ulcer disease, psychoses, pulmonary circulatory disorder, renal failure, rheumatoid arthritis, nonmetastatic tumor, and weight loss), and procedures (prior revascularization, prior catheterization, prior percutaneous coronary intervention [PCI], prior coronary artery bypass graft surgery, cardiac transplant, prior stress test, prior cardiac blood pool imaging, cardiac magnetic resonance imaging, cardiac computed tomography [CT], CT coronary angiography, prior myocardial perfusion imaging, prior transthoracic echocardiogram, and prior transesophageal echocardiogram).

We applied stabilized weights for each patient in the cohort at each time that an event was observed.[23] Treating testosterone therapy as a time-varying covariate, Cox proportional hazards models with stabilized inverse probability of treatment weighting were used to assess the association between testosterone therapy and the primary outcome of death, MI, or stroke. Next, we adjusted for the presence of CAD and then tested for an interaction between CAD status and testosterone therapy. We wanted to determine whether the association of testosterone therapy with adverse outcomes was modified by the presence of CAD given the uncertainty regarding the safety of testosterone therapy in older men with comorbidities such as CAD.

We compared select baseline characteristics between patients receiving testosterone therapy (based on whether testosterone was given at any point during follow-up) and patients not receiving testosterone therapy using *t* tests for continuous variables and Fisher exact tests for dichotomous variables. We also compared the covariate balance of patients prescribed testosterone therapy vs no testosterone therapy based on the cohorts created by the stabilized inverse probability of treatment weighting at 180, 365, and 540 days during follow-up after coronary angiography.[23] *P* values were obtained for the comparison between the testosterone therapy and no testosterone therapy groups to assess covariate balance.

We applied the stabilized inverse probability of treatment weighting to obtain Kaplan-Meier survival curves with testosterone therapy use treated as a time-varying covariate.[24] To further assess the association between testosterone therapy and outcomes, we separated the exposure by type of testosterone prescribed (injections, patch, and gel) and used linear contrasts to evaluate for differences in risk of outcomes across the testosterone preparations.

Next, we performed a series of sensitivity analyses to further assess the robustness of our findings. First, we assessed whether the differences in outcomes could be attributed to differential treatment of cardiovascular risk factors or use of secondary prevention medications between the testosterone therapy vs no testosterone therapy groups. Using stabilized inverse probability of treatment weighting based on the same covariates used in the primary model, we compared low-density lipoprotein (LDL) and blood pressure levels at 1 and 2 years following coronary angiography between patients receiving vs not receiving testosterone therapy at those times using *t* tests. We also compared the proportion of patients filling statins and β-blocker prescriptions at 1 and 2 years following coronary angiography between the testosterone therapy vs no testosterone therapy groups using χ^2 tests with stabilized inverse probability of treatment weighting. Second, we included subsequent coronary revascularization, including PCI and CABG surgery as additional outcomes and assessed the association between testosterone therapy and outcomes (death, stroke, MI, PCI, and CABG surgery). Third, we assessed the dose prescribed and the duration of testosterone treatment based on the dates of testosterone refill as well as the number of refills obtained. Finally, we evaluated the testosterone levels among patients with repeat testosterone levels following initiation of therapy.

R version 2.15.2 (The R Foundation for Statistical Computing, http://www.R-project.org) was used for data preparation and for descriptive and graphical analysis. The Cox regression models for this article were fit using SAS/STAT software, version 9.3 of the SAS System for Windows 2002-2010 (SAS Institute Inc). Hypothesis tests were 2-sided and performed at a .05 significance level.

Results

The primary cohort consisted of 23 173 men who underwent coronary angiography between 2005 and 2011 and who had had a total testosterone level checked (**Figure 1**). We excluded the following patients from this cohort: 2798 patients initiated testosterone prior to coronary angiography; 112 patients who started testosterone prior to having a testosterone level checked; 397 patients who had missing coronary anatomy information; 1132 patients who had testosterone prescribed after MI; 17 patients with hematocrit levels higher than 50%; 12 patients with PSA levels of 4.0 ng/mL or higher; and 9996 patients who had total testosterone levels of 300 ng/dL or higher.

In the cohort of 8709 veterans with a total testosterone level less than 300 ng/dL who underwent coronary angiography, there was a high burden of comorbidities. Approximately 20% had a prior history of MI, 50% had diabetes, and more than 80% had CAD. Of the 8709 patients, 1223 (14.0%) initiated testosterone therapy after a median of 531 days (in-

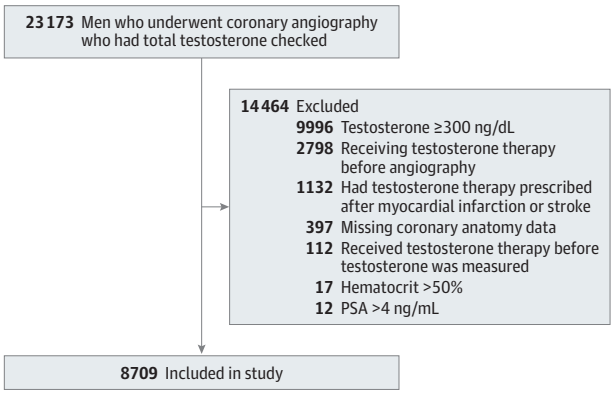
terquartile range [IQR], 229-894 days) following angiography. Patients who initiated testosterone therapy tended to be younger and have lower rates of comorbidities (eg, congestive heart failure and renal failure; **Table 1**).

The average follow-up was approximately 840 days or 27.5 months. Of the 1710 total number of events in the entire cohort, 748 died; 443 had MIs; and 519 had strokes. Of the 7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Of the 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. The absolute rate of events among the no testosterone group vs testosterone therapy at 1 year was 10.1% vs 11.3%; at 2 years, 15.4% vs 18.5%; and at 3 years, 19.9% vs 25.7% after coronary angiography. The absolute risk differences were 1.3% (95% CI, −7.1% to 9.7%) at 1 year, 3.1% (95% CI, −4.9% to 11.0%) at 2 years, and 5.8% (95% CI, −1.4% to 13.1%) at 3 years.

Following application of the standardized weights, there were no statistically significant differences in the comorbidities between the groups at 180, 365, and 540 days of follow-up except for a history of cerebrovascular disease (**Table 2**). Kaplan-Meier survival curves demonstrated that testosterone use was associated with increased risk of death, MI, or stroke (**Figure 2**). The prevalence of the weighted comorbidities at 180, 365 and 540 days among those using and not using testosterone therapy during those time points are presented in the eTable in the Supplement. In analysis with standardized weights and testosterone therapy as a time-varying covariate, testosterone use was associated with increased risk of adverse outcomes including all-cause mortality, MI, and ischemic stroke (hazard ratio [HR], 1.29; 95% CI, 1.05-1.58; $P = .02$). The findings remained unchanged after adjusting for the presence of CAD (HR, 1.29; 95% CI, 1.04-1.58). There was no significant difference in the effect size of testosterone therapy between those with and without CAD (test of interaction, $P = .41$). Furthermore, the association between testosterone therapy and adverse outcomes adjusting for the presence of CAD remained unchanged when revascularization procedures were included as additional outcomes (HR, 1.37; 95% CI, 1.21-1.56).

Of the patients receiving testosterone therapy, 13 (1.1%) were prescribed testosterone gel; 436 (35.7%), injections; and 774 (63.3%), patches. The most common gel dispensed was testosterone 1% 5-g packets; injections, testosterone 200-mg/mL injections; and patch testosterone, 2.5-mg/24-hour

Figure 1. Study Cohort



To convert testosterone from ng/dL to nmol/L, multiply by 0.0347. PSA indicates prostate-specific antigen.

Table 1. Characteristics of Patients at Study Entry Who Did and Did Not Receive Testosterone Therapy

	Unweighted Covariates at Study Entry, No. (%) of Patients		
	No Testosterone Therapy (n = 7486)	Testosterone Therapy (n = 1223)	*P* Value
Age, mean (SD), y	63.8 (9.0)	60.6 (7.6)	<.001
Total testosterone, mean (SD), ng/dL	206.5 (73.8)	175.5 (62.3)	<.001
Coronary arteries			
Normal	900 (12.3)	197 (16.1)	<.001
Nonobstructed	2089 (27.9)	356 (29.1)	.64
Obstructed	4497 (60.1)	670 (54.8)	.001
Hypertension	6952 (92.9)	1101 (90.0)	.001
Hyperlipidemia	6611 (88.3)	1051 (85.9)	.02
Diabetes	4171 (55.7)	650 (53.2)	.09
Obesity	4033 (53.9)	703 (57.5)	.02
Depression	2641 (35.3)	448 (36.6)	.37
Prior PCI	2181 (29.1)	335 (27.4)	.22
Obstructive sleep apnea	1980 (26.4)	341 (27.9)	.30
Congestive heart failure	1826 (24.4)	222 (18.2)	<.001
Prior myocardial infarction	1816 (24.3)	248 (20.3)	.002
Chronic obstructive pulmonary disease	1622 (21.7)	228 (18.6)	.02
Peripheral vascular disease	1463 (19.5)	201 (16.4)	.01
Cerebrovascular disease	1222 (16.3)	136 (11.1)	<.001

Abbreviation: PCI, percutaneous coronary intervention.

SI conversion factors: To convert testosterone from ng/dL to nmol/L, multiply by 0.0347.

Table 2. *P* Values for Stabilized Weighting of Covariate Balance at 180, 365, and 540 Days

	P Values for Weighted Comorbidities Between Testosterone vs No Testosterone Therapy		
	180 d	365 d	540 d
Coronary arteries			
Normal	.64	.82	.45
Nonobstructed	.57	.78	.76
Obstructed	.40	.68	.80
Prior myocardial infarction	.62	.73	.38
Congestive heart failure	.53	.99	.40
Diabetes	.59	.36	.30
Renal failure	.86	.73	.14
Depression	.82	.52	.97
Prior PCI	.69	.96	.79
Hyperlipidemia	.41	.68	.98
Peripheral vascular disease	.85	.42	.55
Chronic obstructive pulmonary disease	.81	.50	.34
Obesity	.26	.25	.12
Hypertension	.98	.61	.63
Cerebrovascular disease	.79	.02	.004
Obstructive sleep apnea	.71	.92	.93

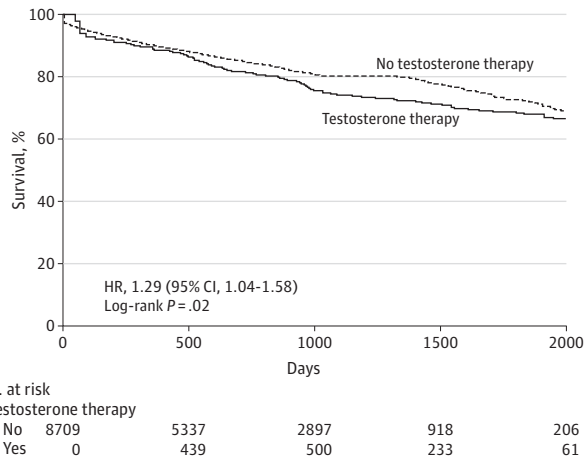
Abbreviation: PCI, percutaneous coronary intervention.

patch. We did not detect a significant difference in the risk of adverse outcomes across the 3 testosterone formulations ($\chi^2_{3.6}$; $P = .17$).

We assessed whether the differences in outcomes between patients receiving vs not receiving testosterone therapy could be related to differential treatment of cardiovascular risk factors or use of secondary prevention medications (**Table 3**). There were no significant differences in systolic blood pressures at 1 and 2 years. The mean diastolic blood pressure at year 1 for patients receiving testosterone was lower than for patients who were not but was not different at 2 years. No significant differences in LDL levels or in use of β-blockers and statin medications existed at 1 and 2 years between groups.

Of the 1223 patients prescribed testosterone therapy, 215 patients (17.6%) filled only 1 prescription and 1008 (82.4%) filled more than 1 prescription for testosterone therapy. Of the patients with more than 1 filled prescription, the mean number of days from first fill to the last fill of testosterone therapy was 376 days. Furthermore, the mean numbers of refills by testosterone formulation were 9.8 for gel, 11.2 for injections, and 6 for patches. Of the patients prescribed testosterone therapy, 734 patients (60.0%) had another testosterone value checked after starting treatment. These patients had a mean of 3.3 measurements. Among these patients, the baseline testosterone level was 175.5 ng/dL and increased to 332.2 ng/dL for the first repeat testosterone measurement.

Figure 2. Kaplan-Meier Survival Curves With Testosterone Therapy Evaluated as a Time-Varying Covariate



Discussion

The objective of this study was to assess the association between testosterone therapy and all-cause mortality, MI, or ischemic stroke. The use of testosterone therapy was significantly associated with adverse outcomes despite the lower prevalence of baseline comorbidities in the testosterone therapy group. The association was consistent among patients with and without CAD. The increased risk of adverse outcomes associated with testosterone therapy use was not related to differences in risk factor control or rates of secondary prevention medication use because patients in both groups had similar blood pressure, LDL levels, and use of secondary prevention medications. These findings raise concerns about the potential safety of testosterone therapy.

Clinical trials have demonstrated that testosterone therapy improves a number of intermediate outcomes and cardiac risk factors. Aside from the TOM trial,[16] these trials and subsequent meta-analyses[25-27] did not demonstrate adverse cardiovascular outcomes. However, most of the studies were small, enrolled patients of different ages, and were of variable duration. A clinical trial evaluating the effect of testosterone therapy

Table 3. Blood Pressure, Low-Density Lipoprotein Levels, and Use of Statins and β-Blockers Among Patients After Coronary Angiography

	No Testosterone Therapy	Testosterone Therapy	*P* Value
Blood pressure, mean (SD), mm Hg[a]			
1 Year			
Systolic	130.9 (21.0)	129.2 (10.25)	.10
Diastolic	74.6 (13.1)	73.1 (6.9)	.02
2 Years			
Systolic	130.7 (20.7)	130.0 (14.2)	.47
Diastolic	74.5 (13.0)	73.4 (9.4)	.06
LDL, mean (SD), mg/dL[a]			
1 Year	85.4 (41.1)	83.7 (22.0)	.46
2 Years	85.6 (40.9)	85.9 (29.0)	.84
β-Blocker use, No./total (%)			
1 Year	6347.75/7075.87 (89.7)	105.85/119.09 (88.9)	.76
2 Years	4081.83/4527.06 (90.2)	249.23/280.14 (89.0)	.51
1 Year statin use, No./total (%)[b]	6649/7075.87 (94.0)	110.8/119.09 (93.0)	.67

SI conversion factor: To convert LDL from mg/dL to mmol/L, multiply by 0.0259.

[a] The blood pressure and low-density lipoprotein value closest to 1 and 2 years following angiography were used.

[b] β-Blocker and statin use was identified by a filled prescription plus or minus 90 from 1 and 2 years following angiography.

on cardiovascular outcomes including mortality, MI, and stroke has not been conducted to our knowledge. The TOM study,[16] which enrolled an older cohort of men with a high prevalence of comorbidities, was halted after enrolling 209 of the planned 252 patients over a 3-year period because 23 patients in the treatment group vs 5 in the placebo had adverse cardiovascular events. Because the long-term safety of testosterone therapy has not been studied, the results of this retrospective study of male veterans add to our understanding of the potential risks of testosterone therapy.

The association between testosterone therapy use and adverse outcomes observed in this study differs from the association observed in a prior retrospective VA study. These discrepant results may be due to differences in the patient populations and methods used to control for confounding. In the study by Shores et al,[28] investigators noted a 39% reduction in mortality risk among patients treated with testosterone therapy. The patients in that cohort had a lower incidence of heart disease (~ 20%) defined by angina, MI, CAD, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, or heart failure. This contrasts with our cohort in which more than 20% had a prior history of MI and heart failure, and more than 50% had confirmed obstructive CAD on angiography. Additionally, the Shores study adjusted for confounders using proportional hazards regression and then used propensity matching in a secondary analysis. This matching method does not account for differences in time from study cohort entry to testosterone initiation, which might not account appropriately for either time-varying treatment-selection bias, immortal time bias, or both.[29] In contrast, the stabilized weights method used in this analysis adjusts for confounders dynamically throughout the study period to overcome these biases.

There are several potential mechanisms by which testosterone therapy may increase cardiovascular risk. First, in a study of healthy men, intramuscular testosterone was associated with an increase in platelet thromboxane A_2 receptor density and platelet aggregation.[30] It is known that platelets play a role in coronary plaque formation, beginning with platelet adhesion and eventual thrombus formation with plaque rupture resulting in acute coronary syndrome.[31] Second, laboratory studies have demonstrated that dihydrotestosterone, a testosterone metabolite, increases smooth muscle proliferation and expression of vascular cell adhesion molecule 1, which enhances monocyte activation in the endothelium.[32,33] Monocytes promote atherosclerosis through their effects on inflammatory cytokines and matrix metalloproteinases and are implicated in the pathogenesis of acute coronary syndromes.[34] Testosterone administration has been shown to worsen sleep disordered breathing among patients with severe obstructive sleep apnea,[35] which is a risk factor for atherosclerosis.[36] Therefore, there are several potential mechanisms by which testosterone therapy could confer increased risk of adverse cardiovascular outcomes, so further study of these mechanisms is needed.

This study is the first observational study, to our knowledge, to suggest that testosterone therapy is associated with adverse cardiovascular outcomes. Our findings raise some uncertainty regarding the potential safety of testosterone use in men. Although physicians should continue to discuss the symptomatic benefits of testosterone therapy with patients, it is also important to inform patients that long-term risks are unknown and there is a possibility that testosterone therapy might be harmful. Randomized clinical trials and observational studies in other populations are needed to help inform whether long-term testosterone therapy use is safe or if it is associated with adverse cardiovascular events.

Potential limitations of this study should be noted. First, given that this was an observational study, unmeasured confounding or hidden bias might exist. However, to minimize residual confounding, we used a nonparsimonious model to obtain stabilized weights in order to balance the covariates among patients receiving and not receiving treatment over the course of the study. Furthermore, we performed several ancillary analyses that showed that no differences existed in risk factor control or use of secondary prevention medications among groups, suggesting that these factors are unlikely to explain the higher event rates in the testosterone therapy group.

Second, we were unable to determine the time of day in which the total testosterone levels were drawn. If some patients had their blood drawn after the morning hours when testosterone levels peak, their levels would be underestimated.[37] There may be small differences in the testosterone assays used by the different VA hospitals that could possibly contribute to error in our assessment of patient's total testosterone levels.

Third, because of the retrospective nature of this study, outcomes were determined using *ICD-9* codes and not validated by chart review. However, *ICD-9* codes have been shown to be valid in determining outcomes including stroke and MI in VA cohorts.[38-40]

Fourth, there was a relatively small group of patients with extended follow-up time (267 patients at 2000 days after coronary angiography) so that our estimates of the risk of testosterone therapy are less reliable at these extremes of follow-up; however, this is a potential limitation of any study that follows up patients for extended periods.

Fifth, this was a select group of patients who were undergoing angiography in the VA system. Although this limits generalizability, we were able to better assess the burden of CAD and evaluate whether the association between testosterone therapy and adverse outcomes was modified by the presence of CAD in response to concerns of a prior randomized clinical trial of testosterone therapy.[16]

Conclusion

Use of testosterone therapy in this cohort of veterans with significant medical comorbidities was associated with increased risk of mortality, MI, or ischemic stroke. These findings were not modified by the presence of CAD. Future studies including randomized controlled trials are needed to properly characterize the potential risks of testosterone therapy in men with comorbidities.

ARTICLE INFORMATION

Author Contributions: Drs Vigen and Ho had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Vigen, O'Donnell, Bradley, Barqawi, Ho.
Acquisition of data: O'Donnell, Plomondon, Rumsfeld, Ho.
Analysis and interpretation of data: Vigen, O'Donnell, Barón, Grunwald, Maddox, Bradley, Barqawi, Woning, Wierman, Plomondon, Ho.
Drafting of the manuscript: Vigen, O'Donnell, Woning, Ho.
Critical revision of the manuscript for important intellectual content: O'Donnell, Barón, Grunwald, Maddox, Bradley, Barqawi, Woning, Wierman, Plomondon, Rumsfeld.
Statistical analysis: Vigen, O'Donnell, Barón, Grunwald.
Administrative, technical, or material support: Woning, Plomondon, Rumsfeld, Ho.
Study supervision: Barqawi.

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