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Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy

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Abstract

Background—Testosterone therapy for older men has increased substantially over the past decade. Research on the effects of testosterone therapy on cardiovascular outcomes has yielded inconsistent results.

Objective—To examine the risk of myocardial infarction (MI) in a population-based cohort of older men receiving intramuscular testosterone.

Method—Using a 5% national sample of Medicare beneficiaries, we identified 6355 patients treated with at least 1 injection of testosterone between January 1, 1997, and December 31, 2005. We matched this cohort to 19 065 testosterone nonusers at a 1:3 ratio based on a composite MI prognostic score. Patients were followed until December 31, 2005, or until they lost coverage from Medicare, enrolled in a health maintenance organization, experienced a MI, or died.

Result—In a Cox regression analysis adjusting for demographic and clinical characteristics, receipt of testosterone therapy was not associated with an increased risk of MI (hazard ratio [HR] = 0.84; 95% CI = 0.69–1.02). In this analysis, there was an interaction between receipt of testosterone and quartile of risk of MI ($P = 0.023$). For men in the highest quartile of the MI prognostic score, testosterone therapy was associated with a reduced risk of MI (HR = 0.69; 95% CI = 0.53–0.92), whereas there was no difference in risk for the first (HR = 1.20; 95% CI = 0.88–1.67), second (HR = 0.94; 95% CI = 0.69–1.30), and third quartiles (HR = 0.78; 95% CI = 0.59–1.01).

Conclusion—Older men who were treated with intramuscular testosterone did not appear to have an increased risk of MI. For men with high MI risk, testosterone use was modestly protective against MI.

Keywords

testosterone; testosterone replacement therapy; myocardial infarction

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Declaration of Conflicting Interests

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Testosterone prescriptions for older men in the United States have increased more than 3-fold over the past decade.[1] This trend has been driven by increases in directto- consumer marketing[2–8]; the rapid expansion of clinics specializing in the treatment of low testosterone[9]; the development of new drugs and improved delivery mechanisms, particularly dermal gels[8,10]; and the greater diagnostic awareness of primary and secondary hypogonadism.[10]

Despite the widespread promotion and use of testosterone therapy in older men, its risks are not well understood.[10,11–14] Clinical trials examining testosterone therapy have been insufficiently powered to provide definitive evidence of adverse events, particularly cardiovascular outcomes.[14] Two meta-analyses of randomized clinical trials that were conducted through 2004[12,13] and one that assessed both randomized and nonrandomized trials through 2008[14] showed no significant effect on subsequent cardiovascular events. However, a randomized clinical trial conducted in 2009 raised widespread concern after it was stopped early because of a greater occurrence of cardiovascular events in the testosterone-treated arm.[15] In addition, a meta-analysis of randomized clinical trials conducted in 2012[16] reported that testosterone therapy was associated with an increased risk of cardiovascular events. Recently, a retrospective cohort study of men in the Veterans Affairs (VA) health system reported that men receiving testosterone therapy had an increased risk of MI, ischemic stroke, and overall mortality.[17] In view of such broadly conflicting evidence, we sought to assess the influence of treatment with intramuscular testosterone therapy on myocardial infarction (MI) in a population of older male Medicare beneficiaries.

Methods

Study Design

We conducted a retrospective cohort study using enrollment and claims data for a 5% national sample of Medicare beneficiaries. The Centers for Medicare and Medicaid Services selected these beneficiaries based on the eighth and ninth digits (05, 20, 45, 70, 95) of their health insurance claim number. Data files were constructed to include their demographic and enrollment information (denominator file), claims for hospital stays (Medicare Provider Analysis and Review file), outpatient visits (Outpatient Standard Analytic file), and physician services (Medicare carrier claim file). This study was reviewed and approved by the University of Texas Medical Branch Institutional Review Board.

Study Participants

Using the Health Care Procedure Coding System (HCPCS) drug administration codes J0900 (testosterone enanthate, up to 1 cc), J1060 (testosterone cypionate, up to 1 mL), J1070 (testosterone cypionate, up to 100 mg), J1080 (testosterone cypionate, up to 200 mg), J3120 (testosterone enanthate, up to 100 mg), J3130 (testosterone enanthate, up to 200 mg), J3140 (testosterone suspension, up to 50 mg), J3150 (testosterone propionate, up to 100 mg) and S0189 (testosterone pellet, 75 mg), we identified Medicare beneficiaries who were 66 years or older and who were treated with intramuscular testosterone between January 1, 1997, and December 31, 2005. To be classified as a testosterone user, the patient was required to have received one or more testosterone injections during the study period.

We excluded men who were not enrolled in both Medicare part A and part B for the 12 months before the first testosterone injection, who were members of a health maintenance organization any time during the 12 months before the first injection, or who had end-stage renal disease. Men who had used testosterone in the 12 months prior to incident testosterone injection were also excluded.

Prognostic Index Score Development

A prognostic index score for MI risk served as the basis for identifying a matched comparison cohort of men who did not receive intramuscular testosterone therapy. To develop this index, we identified a cohort of men ≥66 years old (n = 376 636) who had 12 months of continuous enrollment in calendar year 2000. This cohort was then randomly divided into a development sample (n = 188 318) and a validation sample (n = 188 318). Based on a review of the literature, we identified a total of 109 medical diagnoses and 22 procedures (clinical classification [CC] codes developed by the Agency for Healthcare Research Quality)[18] to predict the binary outcome—hospitalization with a primary discharge diagnosis of MI in 2001. We removed all the factors that did not have a substantial bivariate association ($P < 0.10$) with the outcome, reducing our total number of CC codes to 85 (67 diagnoses and 18 procedures). We then entered each of the 85 CC codes—along with age, race, Medicaid eligibility, and all possible interaction terms with age—into a forward selection logistic regression model. Using an α of <0.05 as our selection criterion, we identified 30 variables and 3 interaction terms that were predictors of the outcome. This model's *C* statistic was 0.653, and the Hosmer-Lemeshow test statistic showed no violation of model fit. The predictive performance of this prognostic index score in the validation sample yielded similar findings (*C* statistic = 0.645 and Hosmer-Lemeshow test statistic showing no violation of model fit). To confirm these findings, we assessed the incidence of MI according to the prognostic risk score at baseline. The overall rate of having an MI event over 1 year of follow-up in the validation sample was 0.022. This increased by 5-fold across the deciles of predicted probability, from 0.009 (first decile) to 0.054 (tenth decile).

Matching Based on the Prognostic Index Score

The prognostic index score—estimated for each testosterone user and nonuser based on covariates measured during the 12 months before testosterone initiation/index date—served as the basis for matching users and nonusers. The initial study entry (index date) for the pool of potential testosterone nonusers was assigned randomly to match the distribution for the month and year of the first testosterone infusion received by testosterone users. To be included in this pool (n = 571 136), each nonuser was required to have 12 months of continuous enrollment before the matched testosterone initiation date and meet the exclusion criteria described above for the testosterone user cohort. Next, we calculated a logit score based on the MI prognostic score. Using this score, we conducted the nearest-neighborhood match without replacement to select the nonuser based on the closest prognostic score to the testosterone user. We selected the best 3 matches (without replacement) for testosterone users that were within ±0.02 of the MI prognostic logit score. Using this methodology, we were able to find matches (n = 19 065) for 99.9% of the testosterone therapy cohort.

Outcome

The outcome was hospitalization for MI (ICD-9-CM code 410.xx) classified according to the primary ICD-9-CM code listed on the discharge diagnosis.

Statistical Analysis

Multivariable survival analyses were performed using Cox proportional hazards regression, with the dependent variable being time to first occurrence of hospitalization for MI.[19,20] We tested the assumption of proportionality in the Cox model by determining that the logarithm of the baseline cumulative hazard rates and the Schoenfield residuals were proportional to follow-up time.[19,20] Patients were censored at death, loss of Medicare part A or part B coverage, time of enrollment in an health maintenance organization, or the end of the study (ie, December 31, 2005). Patient characteristics and treatment with testosterone were treated as independent variables. We also assessed the doseresponse relationship among testosterone users. After restricting eligibility to users who had a minimum of 12 months of follow-up time and did not experience the outcome during the first year (n = 5329), we estimated the hazard ratio (HR) for hospitalization for MI by cumulative dose of testosterone injections received in the first 12 months. Finally, to assess the robustness of our findings, we conducted sensitivity analyses using different eligibility criteria, follow-up periods, exposure thresholds, and covariate adjustment. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). All statistical tests were 2 sided.

Cox Model

In the Cox model, we included education, the total Elixhauser comorbidity index score, indications for testosterone therapy (fatigue, hypogonadism, osteoporosis, and sexual dysfunction), and quartile of MI prognostic risk score (first, 0.000–0.014; second, 0.013–0.022; third, 0.023–0.051; and fourth, 0.052–0.300).

Results

The baseline characteristics of testosterone therapy users and matched nonusers are presented in Table 1. The distribution of age, race, and education were comparable between test users and nonusers. Testosterone users were substantially more likely to have had a high degree of comorbid disease (total Elixhauser score ≥3) compared with nonusers and a longer average follow-up than nonusers and were more likely to have been diagnosed with each of the 4 indications for testosterone use (fatigue, hypogonadism, osteoporosis, and sexual dysfunction). In addition, we examined the average total number of testosterone injections received by users in the first year (4.4 injections) and over the entire follow-up period (8.2 injections).

Table 2 presents the results of the Cox regression model. After adjusting for potential confounders, testosterone therapy was not associated with risk for MI (HR = 0.84; 95% CI = 0.69–1.02). There was interaction between receipt of testosterone and quartile of MI risk (P = 0.023). Therefore, we estimated the risk of MI associated with testosterone use by MI prognostic risk quartile from the Cox model, including the significant interaction. For patients in the highest quartile, receipt of testosterone therapy was associated with a

decreased risk of MI (HR = 0.69; 95% CI = 0.53–0.92). This effect was not observed in patients in the first (HR = 1.20; 95% CI = 0.88–1.67), second (HR = 0.94; 95% CI = 0.69–1.30), and third quartiles (HR = 0.78; 95% CI = 0.59–1.01). We also conducted multivariable analyses assessing a dose-response association among testosterone users. No increase in hospitalization for MI was observed with increasing cumulative number of testosterone injections in the first year (HR = 0.98; 95% CI = 0.96–1.01).

To assess the robustness of our findings, we conducted a number of sensitivity analyses. First, we examined the Cox model restricting on cohorts of testosterone users who received ≥2 injections of testosterone (n = 8356), ≥3 injections of testosterone (n = 6560), and ≥4 injections of testosterone (n = 5392). Second, because many testosterone users had brief periods of exposure, we examined the matched Cox models using reduced follow-up periods (1 year, 2 years). Third, because men who receive testosterone therapy may be less likely to have health conditions with poor prognoses or a limited life expectancy, we examined models in which we removed all men who died within 6, 12, and 18 months of their drug start or index date. We also conducted analyses in which we removed all men who were in a nursing facility 12 months prior to their drug start/index date through the end of follow-up. In each of these analyses, whenever we removed an individual, we also removed all members of the match. Finally, we examined the model in a large cohort that was not matched using the prognostic MI score. This cohort included all possible nonusers who met the basic study entry criteria and could be matched with testosterone users by index date (n = 571 136). In this analysis, we adjusted for all 30 covariates that comprised the prognostic MI risk score in addition to basic demographic characteristics. In each of the above sensitivity analyses, our primary finding—a nonsignificant HR ranging from 0.65 to 0.87—persisted.

Discussion

In this matched double cohort study of more than 25 000 Medicare beneficiaries, we found that use of intramuscular testosterone therapy was not associated with an increased risk of MI. A dose-response analysis demonstrated no increased risk in MI according to estimated cumulative dose of testosterone. These findings were robust across a range of sensitivity analyses that addressed eligibility criteria, exposure thresholds, follow-up periods, and covariate adjustment. Our results are consistent with 3 meta-analyses of studies that were conducted up to 2008 and reported no significant increases in cardiovascular risks.[12–14] However, our findings are not consistent with a recent meta-analysis of randomized clinical trials of testosterone therapy,[15] the Testosterone in Older Men with mobility limitations (TOM) trial, which was stopped early because of a greater occurrence of cardiovascular events in the testosterone treated arm,[16] or the recent retrospective cohort study of men in the VA health system, which reported an increased risk of MI and stroke among testosterone users.[17] Currently, there is widespread debate regarding the extent to which methodological issues—such as participant eligibility criteria, disease classification, and statistical analysis methods—have contributed to the contrasting findings observed across the clinical trials, observational cohort studies, and meta-analyses that have examined testosterone use and cardiovascular risk.[21–24]

The association between testosterone therapy and cardiovascular disease is complex. There are a number of physiological pathways by which testosterone therapy may either increase or decrease the risk of adverse cardiovascular events.[25] Some investigators have suggested that testosterone therapy may improve cardiovascular health by way of decreasing fat mass, insulin sensitivity, and lipid profile.[26–28] Moreover, testosterone may possess anti-inflammatory and anticoagulant properties that may reduce carotid intima media thickness.[26,28] It is possible that our findings of a protective effect among men in the highest MI prognostic group reflects a process whereby testosterone reduces peripheral vascular resistance, thereby reducing stress on the heart among those who have some degree of coronary artery disease.[29]

There are also mechanisms through which testosterone may increase the risk of cardiovascular disease. These include increases in salt and water retention,[30–32] which can lead to edema, hypertension, and heart failure; increases in the risk for coagulation and platelet aggregation, which can lead to an increased risk of stroke or MI[33]; and the possibility of left ventricular hypertrophy and systolic and diastolic dysfunction.[34,35] Given the broad range of proposed biological pathways, further examination of these mechanisms is important.

Our study has several limitations. First, information on both outcomes and risk factors came from diagnosis codes included in charges for outpatient and hospitalization services. Such diagnoses are not always accurate or complete.[36] Second, Medicare claims during the study period provided no data on other formulations (oral, transdermal patch, gel) of testosterone therapy. Therefore, we were unable to assess the extent to which use of these formulations contributed to the outcome. However, given that the prevalence of these 3 formulations combined is estimated to be <1% during this period,[1] it is unlikely that this would have caused a high degree of misclassification in our study cohort. It is also possible that testosterone administered through intramuscular injection may have toxicities that are different from other formulations. In addition, our data did not permit assessment of medications that are associated with reduced risk of MI, such as antilipid or antihypertensive medications. It is possible that men who received testosterone therapy were more likely to have also received cardiovascular preventive medications. Third, prescription claims data do not capture information on pharmaceutical agents purchased outside the plan. Given the perceived social stigma associated with receiving testosterone therapy, some men may choose to seek treatment outside their usual health care setting. Fourth, information on baseline testosterone level was not available in the Medicare claims data. Given that low endogenous testosterone may be associated with an increased risk of cardiovascular disease,[25] failure to account for this baseline risk could increase the likelihood of observing a spurious positive association between testosterone exposure and MI. Fifth, given the retrospective nature of this study, it is possible that undetected selection bias may have affected the findings. For example, older men who use testosterone therapy may have been more likely than their peers to have engaged in positive health behaviors (eg, diet and exercise). In addition, studies have shown that older adults who are prescribed preventive medications, such as testosterone therapy, are less likely to have health conditions with poor prognoses and limited life expectancy.[37] Alternatively, testosterone therapy could affect the clinical presentation of an MI or the patient's behavior when experiencing symptoms,

thereby affecting the MI hospitalization rate but not the rate of MI. Although such factors are difficult to measure using retrospective claims data, our use of matching, multivariable adjustment and sensitivity analyses help address these issues.

Despite these limitations, we believe that this study has important strengths, including a large sample size, a long follow-up period, representation of all US geographic regions, and inclusion of a clinically and socioeconomically diverse cohort. In view of the large increase in the use of testosterone therapy in recent years,[1] examining the shortand long-term risks of testosterone therapy holds increasing clinical and public health relevance. Future research, both observational studies and randomized clinical trials, should be conducted to further examine potential adverse effects of testosterone therapy.

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Table 1

Baseline Demographic and Clinical Characteristics for Intramuscular Testosterone Users and Matched Nonusers.

Characteristic[a]	Testosterone Therapy, n (%) or Mean (SD)	No Testosterone Therapy,[b] n (%) or Mean (SD)
All	6355 (100)	19 065 (100)
Average duration of follow-up (days)	1495 (988.3)	1193 (928.4)
Number of injections in first year		
Mean	4.4 (5.2)	—
1	2395 (37.7)	
2	960 (15.1)	
3	611 (9.6)	
≥4	467 (7.4)	
Number of injections in the entire study period		
Mean	8.2 (16.0)	—
1	2201 (34.6)	
2	932 (14.7)	
3	577 (9.1)	
≥4	2645 (41.6)	
Age (years) at testosterone initiation/index date		
65–69	1996 (31.4)	5079 (26.6)
70–74	1944 (30.6)	5808 (30.5)
75–79	1311 (20.6)	3842 (20.2)
≥80	1104 (17.4)	4336 (22.7)
Race		
White	5984 (93.6)	17 428 (91.4)
Black	344 (5.4)	1304 (6.8)
Hispanic	93 (0.4)	16 (0.1)
Other	63 (1.0)	333 (1.8)
Education (percentage high school education)[c]		
Q1: <8.5	194 (3.1)	2650 (13.9)
Q2: 8.5 to 13.6	1546 (24.3)	3952 (20.7)
Q3: 13.6 to <20.2	1693 (26.6)	4129 (21.7)
Q4: ≥20.2	1518 (23.9)	4236 (22.2)
Unknown	1404 (22.1)	4098 (21.5)
Total Elixhauser score		
0	1335 (21.0)	8075 (42.4)
1	1292 (20.3)	4227 (22.2)
2	1173 (18.5)	2753 (14.4)
≥3	2555 (40.2)	4010 (21.0)
Indications for testosterone		
Fatigue	1895 (29.8)	2723 (14.3)

Characteristic[a]	Testosterone Therapy, n (%) or Mean (SD)	No Testosterone Therapy,[b] n (%) or Mean (SD)
Hypogonadism	2646 (41.6)	72 (0.4)
Osteoporosis	415 (6.5)	338 (1.7)
Sexual dysfunction	3618 (56.9)	703 (3.7)
AHRQ Clinical Classification Codes[d]		
Acute myocardial infarction	115 (1.8)	244 (1.3)
Acute cerebrovascular disease	187 (2.9)	546 (2.9)
Aortic, peripheral, visceral artery aneurysms	123 (1.9)	235 (1.2)
Cardiac dysrhythmia	989 (15.6)	2404 (12.6)
Cardiac stress test	26 (0.4)	76 (0.4)
Chest pain	361 (5.7)	840 (4.4)
Chronic obstructive pulmonary disease (COPD)	695 (10.9)	1453 (7.6)
Coagulation and hemorrhagic disorders	194 (3.1)	426 (2.2)
Complication of device, implant, or graft	100 (1.6)	239 (1.3)
Complications of surgical procedures, medical care	54 (0.8)	106 (0.6)
Congestive heart failure	345 (5.4)	988 (5.2)
Coronary atherosclerosis and other heart disease	1636 (25.7)	3658 (19.2)
Delirium, dementia, cognitive disorders	116 (1.8)	551 (2.9)
Diabetes without complications	1250 (19.7)	2897 (15.2)
Extracorporeal circulation auxiliary to open heart procedure	63 (1.0)	164 (0.9)
Gangrene	2 (0.0)	34 (0.2)
Hemodialysis	14 (0.2)	51 (0.3)
Kidney disease	66 (1.0)	200 (1.0)
Lipid disorder	2156 (33.9)	4180 (21.9)
Lung disease	26 (0.4)	41 (0.2)
Multiple myeloma	22 (0.4)	45 (0.2)
Non-Hodgkin’s lymphoma	98 (1.5)	197 (1.0)
Other diseases of kidney ureters	178 (2.8)	390 (2.1)
Peripheral and visceral atherosclerosis	365 (5.7)	773 (4.1)
Septicemia	50 (0.8)	168 (0.8)
Thyroid cancer	7 (0.0)	8 (0.1)

[a] All study characteristics exhibited differences between testosterone users and nonusers that were statistically significant at >.0001.

[b] We matched 99.9% of testosterone nonusers to users based on an MI prognostic score using the nearest neighborhood match without replacement.

[c] Based on US Census data, the percentage of all persons aged ≥25 years in the patient’s zip code region who have <12 years of education.

[d] Clinical classification codes developed by the Agency for Healthcare Research Quality (AHRQ).[18]

Table 2

Adjusted HRs for MI Requiring Hospitalization Associated With Intramuscular Testosterone Use Among 6353 Male Patients Treated With Testosterone, Compared With 19 065 Matched Controls.

Characteristic	HR	95% CI
Testosterone therapy		
No	1.00	(Referent)
Yes	0.84	0.71, 1.05
Education (percentage <high school education)[a]		
Q1: <8.5	1.00	(Referent)
Q2: 8.5 to 13.6	1.23	1.04, 1.45
Q3: 13.6 to <20.2	1.30	1.10, 1.53
Q4: ≥20.2	1.36	1.16, 1.60
Unknown	1.01	0.78, 1.31
Total Elixhauser score (per 1 unit)	1.01	0.98, 1.04
Indications for testosterone		
Hypogonadism	0.85	0.67, 1.07
Sexual dysfunction	0.84	0.69, 1.02
Osteoporosis	0.94	0.86, 1.62
Fatigue	0.93	0.96, 1.30

Abbreviations: HR, hazard ratio; MI, myocardial infarction.

[a]Based on US Census data, the percentage of all persons aged ≥25 years in the patient's zip code region who have <12 years of education.