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ORIGINAL RESEARCH

Association Between Testosterone Treatment and Risk of Incident Cardiovascular Events Among US Male Veterans With Low Testosterone Levels and Multiple Medical Comorbidities

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BACKGROUND: Testosterone treatment is common in men, although risks for major cardiovascular events are unclear.

METHODS AND RESULTS: A study was conducted in US male veterans, aged ≥40 years, with low serum testosterone and multiple medical comorbidities and without history of myocardial infarction, stroke, venous thromboembolism, prostate cancer, or testosterone treatment in the prior year. For the primary outcome, we examined if testosterone treatment was associated with a composite cardiovascular outcome (incident myocardial infarction, ischemic stroke, or venous thromboembolism). Testosterone use was modeled as intramuscular or transdermal and as current use, former use, and no use. Current testosterone users were compared with former users to reduce confounding by indication. The cohort consisted of 204 857 men with a mean (SD) age of 60.9 (9.9) years and 4.7 (3.5) chronic medical conditions. During follow-up of 4.3 (2.8) years, 12 645 composite cardiovascular events occurred. In adjusted Cox regression analyses, current use of transdermal testosterone was not associated with risk for the composite cardiovascular outcome (hazard ratio [HR], 0.89; 95% CI, 0.76–1.05) in those without prevalent cardiovascular disease, and in those with prevalent cardiovascular disease was associated with lower risk (HR, 0.80; 95% CI, 0.70–0.91). In similar analyses, current use of intramuscular testosterone was not associated with risk for the composite cardiovascular outcome in men without or with prevalent cardiovascular disease (HR, 0.91; 95% CI, 0.80–1.04; HR, 0.98; 95% CI, 0.89–1.09, respectively).

CONCLUSIONS: In a large cohort of men without a history of myocardial infarction, stroke, or venous thromboembolism, testosterone treatment was not associated with increased risk for incident composite cardiovascular events.

Key Words: cohort study ■ myocardial infarction ■ stroke ■ testosterone ■ thrombosis

Testosterone prescriptions in the United States increased rapidly from 2000 to 2013 associated with direct-to-consumer advertising.[1–3] However, safety concerns developed after studies reported increased cardiovascular events,[4–6] increased cardiovascular events with intramuscular testosterone,[5,7–9] and that cardiovascular events occurred shortly after testosterone was initiated.[5,10–14] However, other studies failed to detect overall cardiovascular risks,[7–9,15–25] and regulatory agencies issued

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CLINICAL PERSPECTIVE

What Is New?

- Using a database of a large, well-characterized cohort, we examined the risk of both composite major cardiovascular outcomes (myocardial infarction, stroke, thrombosis) and respective components separately among men with low testosterone levels and without testosterone treatment at baseline, and examined risks associated with testosterone initiation.
- Among men with low testosterone levels, the current use of intramuscular and transdermal testosterone (compared with previous use) was not associated with increased risk for composite or separate cardiovascular outcomes, regardless of whether they have cardiovascular disease or not.

What Are the Clinical Implications?

- The results from this large cohort study provide some reassurance that testosterone treatment does not appear to be associated with significant risk for major cardiovascular events.
- However, because of the observational study design and nonrandomization to treatment, residual confounding cannot be excluded, and a large, randomized, double-blind, placebo-controlled trial is needed to definitively assess the cardiovascular risks of testosterone.
- Until a large, randomized trial has been completed, clinicians should follow testosterone treatment guidelines and carefully review specific risks and benefits of testosterone treatment with patients.

Nonstandard Abbreviations and Acronyms

VA	Veterans Affairs
VHA	Veterans Health Administration

contradictory assessments of cardiovascular risks of testosterone treatment.[26–28] The conflicting results of prior studies may be attributable to cohorts with different cardiovascular morbidity and gonadal status (eugonadal, hypogonadal, or unknown). Another limitation has been the use of testosterone exposure models that characterized testosterone use as any use versus no use.[4,8,12,16,19,23,24] Although this model is often used in pharmaco-epidemiologic studies, it is limited by an inability to account for intermittent or discontinued treatment or to ascertain whether cardiovascular events occurred during testosterone use. The objective of this study was to determine if testosterone treatment was associated with risk for major cardiovascular events in men with age-related low testosterone. We examined the association of testosterone treatment with a composite cardiovascular end point composed of major, new-onset cardiovascular events of myocardial infarction (MI), ischemic stroke, and venous thromboembolism (VTE). We addressed limitations of prior studies by modeling testosterone exposure as current use and former use to account for intermittent treatment and to ascertain if cardiovascular events occurred with current use of testosterone. We hypothesized that any potential risks associated with testosterone were attributable to a "drug-in-the-blood" effect and that highest risk would occur during current use of testosterone.

METHODS

Design and Data Source

We conducted a cohort study of men with low serum testosterone who were followed for testosterone initiation and incident cardiovascular events. We collected data from the Veterans Health Administration (VHA), the largest integrated healthcare system in the United States, and from the Centers for Medicare and Medicaid Services. The data from the VHA Corporate Data Warehouse included demographics, laboratory data, pharmacy data, diagnostic codes (*International Classification of Diseases, Ninth Revision* [*ICD-9*]), and procedure codes (Current Procedural Terminology).[29] The Centers for Medicare and Medicaid Services data included diagnostic codes for MI, ischemic stroke, VTE, and prescription data (testosterone and anticoagulants). The Department of Veterans Affairs (VA) Institutional Review Board in Seattle, Washington, approved this study and waived the requirement for informed consent. Data sharing is not permitted by the VA. However, all source data for the study are available through the VA and can be accessed with proper VA Research and Development regulatory approvals.

Study Cohort

The cohort included male veterans aged 40 to 89 years with low serum testosterone measured between January 1, 2002, and December 31, 2011; at least 2 clinic visits in the prior year, no testosterone treatment or prostate-specific antigen ≥4.0 ng/dL in the prior year; and no history of prostate or breast cancer as these are exclusions in testosterone treatment studies. Men were classified as having low serum testosterone if they had a testosterone measure flagged as low by the testing laboratory. Subjects with missing race, body mass index (BMI), or region were excluded from the analysis. Additional restrictions in the study cohort are specific to individual analyses; see Outcomes below.

Testosterone Exposure and Follow-up Levels

Prescription data included testosterone formulation, fill date, and prescription duration. Testosterone formulations consisted of intramuscular and transdermal testosterone. Intramuscular formulations were primarily intermediate-acting testosterone (enanthate or cypionate) and transdermal formulations were testosterone patch or gel. Intramuscular and transdermal testosterone formulations were tracked separately. For each formulation, we modeled time-varying testosterone exposure as current use (current filled prescription), former use (prior prescription during the study, but no current filled prescription for that formulation), or no use (no testosterone prescription filled during the study). All subjects were nonusers of testosterone when they entered the cohort and became current users on the date a testosterone prescription was filled. Current use lasted for the prescription duration plus a 20% overrun of the prescription duration to account for refill time, noncompliance, or residual effects. Testosterone treatment status was continuously updated during the study, so that a subject could switch from current use to former use and then back to current use for each formulation. Follow-up total testosterone levels were summarized for current testosterone users and nonusers who had testosterone levels assessed during the year after cohort entry.

Outcomes

The primary outcome was an incident composite cardiovascular end point, composed of incident MI, ischemic stroke, or VTE (pulmonary embolism or deep venous thrombosis). Men were excluded from the primary outcome if they had prior diagnoses of MI, ischemic stroke, or VTE. Secondary analyses considered separate outcomes of MI, ischemic stroke, and VTE. Men were excluded from the secondary analyses if they had a prior event of that type; for example, men with a history of MI were excluded from the MI analysis but were included in the VTE and stroke analyses. Cardiovascular outcomes were identified using inpatient diagnostic codes (from VHA and Centers for Medicare and Medicaid Services data), procedure codes, and medications (Table S1).

Medical Comorbidities

We characterized baseline and emerging medical conditions (diagnosed after cohort entry) using *ICD-9* diagnostic and procedure codes, Current Procedural Terminology procedure codes, medications, and laboratory results (Table S2). The medical comorbidities were time-varying covariates that could change from absent to present over the course of the study but, once identified as present, were maintained as present. For example, once a patient was identified as having diabetes mellitus, they were classified as having diabetes mellitus for the remainder of the study. Medical comorbidities included chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, sexual dysfunction, hyperlipidemia, hypertension, major depression, morbid obesity, polycythemia, sleep apnea, smoking, and prevalent cardiovascular disease (CVD). Prevalent CVD included arrhythmia, angina, coronary artery disease, chronic heart failure, cardiomyopathy, peripheral vascular disease, cerebrovascular disease, transient ischemic attack, and cardiovascular procedures (angioplasty, bypass, stent placement). In secondary analyses for separate outcomes, prevalent CVD also included MI, ischemic stroke, or VTE except in analyses for that specific outcome. Finally, in analyses for VTE and the composite end point, we adjusted for malignancy (excluding basal cell skin cancer).

Statistical Analysis

We conducted Cox regression analyses to estimate the association between testosterone treatment and an incident composite cardiovascular end point and, in secondary analyses, the association of testosterone treatment with separate outcomes of incident MI, stroke, or VTE. The assumption of proportional hazards was confirmed via Schoenfeld residuals. Cohort entry was the date of the first low serum testosterone measure. Men were followed until a cardiovascular event, death, or end of follow-up (September 30, 2012). Testosterone treatment was modelled separately for intramuscular and transdermal testosterone and updated continuously. Men who were current users of testosterone were compared with former users to reduce confounding by indication. In the regression analyses, we adjusted for baseline covariates and for emerging medical conditions that occurred following cohort entry. At baseline, we adjusted for age, race, region, year of cohort entry, BMI, hospitalization, medical comorbidities, and prevalent CVD. For conditions that occurred after baseline, we used time-varying adjustments for hospitalization, medical comorbidities, and prevalent CVD. We also estimated how treatment effects varied by presence of CVD by including an interaction between time-varying testosterone treatment status and CVD. In sensitivity analyses, we examined results using different definitions of current testosterone treatment that consisted of prescription duration plus an overrun ranging from 0% to 40% of the prescription duration. We also examined risk associated with testosterone initiation by comparing incidence rates for events in men with continuous treatment at 3, 6, and 12 months following testosterone initiation to the

Table 1. Baseline Characteristics of Men in the Analytic Cohort

	No use (N=122 302)	Initiated with transdermal testosterone (N=43 502)	Initiated with intramuscular testosterone (N=39 053)	All (N=204 857)
Age, y, mean (SD)	61.7 (10.2)	59.8 (9.4)	59.3 (9.2)	60.9 (9.9)
Age, y, n (%)				
40–49	14 228 (11.6)	5969 (13.7)	5684 (14.6)	25 881 (12.6)
50–59	37 748 (30.9)	15 411 (35.4)	14 433 (37.0)	67 592 (33.0)
60–69	44 315 (36.2)	15 933 (36.6)	13 924 (35.6)	74 172 (36.2)
70–79	18 470 (15.1)	4775 (11.0)	3985 (10.2)	27 230 (13.3)
80–89	7541 (6.2)	1414 (3.3)	1027 (2.6)	9985 (4.9)
Cohort entry year, n (%)				
2002–2003	18 539 (15.2)	6412 (14.7)	7111 (18.2)	32 062 (15.7)
2004–2005	15 903 (13.0)	6246 (14.3)	5525 (14.2)	27 674 (13.5)
2006–2007	18 147 (14.8)	6733 (15.5)	6332 (16.2)	31 212 (15.2)
2007–2009	27 229 (22.3)	10 252 (23.6)	8575 (22.0)	46 056 (22.5)
2010–2011	42 484 (34.7)	13 859 (31.9)	11 510 (29.5)	67 853 (33.1)
Region of United States, n (%)				
Western	27 686 (22.6)	7068 (16.2)	12 830 (32.9)	47 584 (23.3)
Upper Midwest	12 923 (10.6)	5297 (12.2)	2490 (6.4)	20 710 (10.1)
Upper middle and eastern	22 321 (18.3)	5746 (13.2)	8090 (20.7)	36 157 (17.6)
Northeastern	16 349 (13.4)	7352 (16.9)	2036 (5.2)	25 737 (12.6)
Southern	43 023 (35.2)	18 039 (41.5)	13 607 (34.8)	74 669 (36.4)
BMI, mean (SD)	31.5 (6.7)	32.6 (6.7)	32.8 (6.7)	32.0 (6.7)
BMI, n (%)				
<18.5	1405 (1.1)	343 (0.8)	223 (0.6)	1971 (1.0)
18.5–24.9	15 844 (13.0)	4059 (9.3)	3263 (8.4)	23 166 (11.4)
25–29.9	37 139 (30.4)	11 895 (27.2)	10 623 (27.2)	59 657 (29.1)
30–34.9	36 079 (29.5)	13 558 (31.8)	12 425 (31.8)	62 062 (30.3)
>35	31 835 (26.0)	13 647 (31.4)	12 519 (32.1)	58 001 (28.3)
Race, n (%)				
White	97 589 (79.8)	35 548 (81.7)	33 158 (84.9)	166 295 (81.2)
Black	21 102 (17.3)	6722 (15.5)	4609 (11.8)	32 433 (15.8)
Other*	3611 (3.0)	6722 (2.8)	1286 (3.3)	6129 (3.0)
Prevalent cardiovascular disease, n (%)	50 292 (41.1)	16 481 (37.9)	14 441 (37.0)	81 214 (39.6)
Arrhythmia	20 813 (17.0)	6309 (14.5)	5869 (15.0)	32 991 (16.1)
Cardiomyopathy	3681 (3.0)	1146 (2.6)	814 (2.1)	5641 (2.8)
Coronary artery disease or angina	32 055 (26.2)	10 390 (23.9)	8914 (22.8)	51 359 (25.1)
Ischemic cerebrovascular disease or TIA	4690 (3.8)	1494 (3.4)	1137 (2.9)	7321 (3.6)
Chronic heart failure	9949 (8.1)	2978 (6.8)	2177 (5.6)	15 104 (7.4)
Peripheral vascular disease	11 626 (9.5)	3539 (8.1)	2885 (7.4)	18 050 (8.8)
Myocardial infarction	3904 (3.2)	1127 (2.6)	900 (2.3)	5931 (2.9)
Stroke, ischemic	1800 (1.5)	490 (1.1)	342 (0.9)	2632 (1.3)
VTE (DVT and PE)	1175 (1.0)	388 (0.9)	248 (0.6)	1811 (0.9)
Medical comorbidities, n (%)				
Chronic kidney disease	6837 (5.6)	1790 (4.1)	1376 (3.5)	10 003 (4.9)
Chronic lung disease	24 643 (20.2)	8239 (18.9)	7166 (18.4)	40 048 (19.5)
Diabetes mellitus	40 983 (33.5)	14 058 (32.3)	12 063 (30.9)	67 104 (32.8)

(*Continued*)

Table 1. Continued

	No use (N=122 302)	Initiated with transdermal testosterone (N=43 502)	Initiated with intramuscular testosterone (N=39 053)	All (N=204 857)
Erectile dysfunction	46 158 (37.7)	18 585 (42.7)	16 790 (43.0)	81 533 (39.8)
Hospitalization in prior year	20 421 (16.7)	6240 (14.3)	4952 (12.7)	31 613 (15.4)
Hyperlipidemia	36 008 (29.4)	13 558 (31.2)	11 531 (29.5)	61 097 (29.8)
Hypertension	76 665 (62.7)	26 661 (61.3)	23 118 (59.2)	126 444 (61.7)
Major depression	19 284 (15.8)	7923 (18.2)	7388 (18.9)	34 595 (16.9)
Malignancy	17 667 (14.5)	5813 (13.4)	4750 (12.2)	28 230 (13.8)
Morbid obesity	8497 (7.0)	3467 (8.0)	3095 (7.9)	15 059 (7.3)
Polycythemia	447 (0.4)	130 (0.3)	146 (0.4)	723 (0.4)
Sleep apnea	18 627 (15.2)	7806 (17.9)	7145 (18.3)	33 578 (16.4)
Smoking	35 963 (29.4)	12 424 (28.6)	10 957 (28.1)	59 344 (29.0)
No. of comorbidities, mean (SD)	4.8 (3.6)	4.7 (3.5)	4.5 (3.4)	4.7 (3.5)
Serum total testosterone, ng/dL, mean (SD)	210 (126)	174 (83)	173 (76)	195 (111)

Note that medical comorbidities were identified using *ICD-9* diagnostic and procedure codes, Current Procedural Terminology procedure codes, medications, and laboratory results as outlined in Table S2. DVT indicates deep vein thrombosis; PE, pulmonary embolism; and VTE, venous thromboembolism.*Other includes Alaskan / American Indian, Asian, Hawaiian/Pacific Islander.

overall incidence rate associated with continuous testosterone treatment. Finally, we conducted an exploratory case-crossover investigation for the composite cardiovascular outcome. This analysis used a subject as their own control and examined if current testosterone treatment is more likely at the time of the composite cardiovascular outcome than before the outcome. All analyses were conducted in R version 3.6.1.[30]

RESULTS

We identified 300 631 men, aged 40 to 89 years, with serum testosterone levels that were flagged as low per the testing laboratory. The mean threshold from the testing laboratories for low total testosterone was 220.85 ng/dL and for low free testosterone was 4.58 ng/dL. After a priori exclusions were applied, 204 857 (68%) men remained in the analytic cohort (Figure). Most testosterone measurements in the cohort were for total testosterone (78.0%) and free testosterone (20.8%), while 4.1% were for other testosterone measures. (Percentages add up to more than 100, as some men had multiple low testosterone measures.) Table 1 lists characteristics of testosterone nonusers and transdermal and intramuscular testosterone initiators in the analytic cohort. At baseline, the cohort had a mean (SD) age of 60.9 (9.9) years. The men in the cohort tended to be hypertensive (61.7%) and obese (mean BMI, 32.0 [6.7] kg/m^2) and had chronic medical morbidity with a mean of 4.7 (3.5) chronic medical conditions, with 32.8% of men with diabetes mellitus and 39.6% with prevalent CVD. Over a mean follow-up of 4.3 (2.8) years, 82 555 (40.3%) men filled a testosterone prescription. Of the testosterone-treated men, 38% received only transdermal, 40% only intramuscular, and 22% received both intramuscular and transdermal testosterone at some point, but usually not concurrently. Testosterone treatment time was short, with a median cumulative treatment time of 4.8 months for transdermal and 11.1 months for intramuscular testosterone, with men spending more time as former users than current users of testosterone (Table 2). During follow-up, serum total testosterone increased for nonusers, transdermal, and intramuscular users. Intramuscular testosterone users had a mean testosterone level within the physiologic range, while transdermal testosterone users and nonusers of testosterone had low or low-normal mean testosterone levels (Table 3).

Primary and Secondary Outcomes

During the study, 12 645 composite cardiovascular events occurred. In current and former transdermal

Table 2. Duration of Cumulative Testosterone Treatment Times

Cumulative testosterone treatment time	Transdermal	Intramuscular
Current use, mo	n=49 834	n=50 845
Median (IQR)	4.8 (2.4–10.9)	11.1 (4.8–22.9)
Mean (SD)	9.5 (12.7)	17.4 (18.4)
Former use, mo	n=49 104	n=49 515
Median (IQR)	27.8 (12.4–55.9)	20.3 (7.0–47.7)
Mean (SD)	37.4 (31.1)	31.3 (30.7)

Transdermal-treated men had a shorter duration of testosterone treatment than men who were treated with intramuscular testosterone.

Table 3. Serum Total Testosterone Levels

Total testosterone, ng/dL	Testosterone treatment status		
	No use N=29 954	Transdermal N=5953	Intramuscular N=7337
Baseline, mean (SD)	195 (105)	165 (81)	166 (71)
Baseline, median (IQR)	190 (145–230)	165 (119–210)	170 (125–210)
Follow-up, mean (SD)	276 (167)	312 (212)	455 (321)
Follow-up, median (IQR)	249 (182–330)	260 (173–399)	372 (215–620)

Among treated men, testosterone measures were those obtained during the first year of current treatment. Among untreated men, testosterone levels were those obtained during the first year following cohort entry. If there were multiple levels obtained during the time period, levels were averaged. IQR indicates interquartile range.

users with (without) prevalent CVD, incidence rates were 15.74 and 20.73 (8.68 and 9.62) per 1000 person-years, respectively. In current and former intramuscular users with (without) prevalent CVD, incidence rates were 19.16 and 21.29 (10.03 and 11.03) per 1000 person-years, respectively (Table 4). In fully adjusted Cox regression analyses, current compared with former transdermal use was associated with lower risk of composite cardiovascular events in those with prevalent CVD (hazard ratio [HR], 0.80; 95% CI, 0.70–0.91), and no increased risk was detected in those without prevalent CVD (HR, 0.89; 95% CI, 0.76–1.05), nor in the comparison of current to former intramuscular users with or without prevalent CVD (HR, 0.98; 95% CI, 0.89–1.09; HR, 0.91; 95% CI, 0.80–1.04, respectively). In secondary analyses of separate outcomes of MI, ischemic stroke, and VTE, current transdermal users with prevalent CVD had a lower risk for MI and VTE compared with former users (HR, 0.80; 95% CI, 0.67–0.91; HR, 0.72; 95% CI, 0.55–0.94, respectively). No increased risk of MI, ischemic stroke, or VTE were detected in transdermal users without prevalent CVD, nor in current versus former intramuscular users with or without prevalent CVD (Table 5). In a sensitivity analysis that varied the exposure window for current testosterone (Table S3), our results were largely unchanged, and we found no increased risks associated with testosterone initiation (Table S4). The results of an exploratory case-crossover investigation for the composite cardiovascular outcome also supported our conclusions and detected no increased risk associated with current testosterone treatment (Data S1).

DISCUSSION

In a large cohort of US veterans, aged ≥40 years, with low testosterone and multiple medical comorbidities, we examined cardiovascular risks of current versus former use of transdermal and intramuscular testosterone in multivariable adjusted Cox regression analyses. Over a mean follow-up of 4.3 years, we detected 12 645 incident composite cardiovascular events and found no consistent association of transdermal or intramuscular testosterone with increased risk for an incident composite cardiovascular end point or separate events of incident MI, ischemic stroke, or VTE. We had hypothesized that risk would be greatest during current testosterone treatment, but we did not detect this. In our analyses, we observed that in men with prevalent CVD, current transdermal testosterone was associated with a lower risk of composite cardiovascular events, MI, and VTE compared with former use of transdermal testosterone. We did not hypothesize that testosterone treatment would protect against the risk of cardiovascular events and do not believe the observed association is causal, but rather the result of residual confounding or multiple comparisons. Furthermore, this association was not seen in transdermal-treated men without prevalent CVD nor in men treated with intramuscular testosterone.

Prior Studies

Results of prior cohort studies examining the association of testosterone treatment with cardiovascular events have been conflicting. In studies that examined the risks of testosterone treatment for a composite cardiovascular end point, several studies reported that testosterone treatment was associated with increased risk,[4,12,14] while others reported either no overall risk[9,25] or a decreased risk[18,19] for a composite outcome. However, these studies are difficult to compare as none of them defined the composite cardiovascular end point in the same way (Table S5). All the studies included MI in the composite end point, but they differed on inclusion of stroke, unstable angina, transient ischemic attack, coronary revascularization, sudden cardiac death, postoperative mortality, and total mortality. We defined the composite end point as MI, VTE, and ischemic stroke, as these are major adverse cardiovascular events that have a clinically significant impact. We did not include revascularization procedures, as these may be influenced by local practice patterns; or total mortality and postoperative mortality,

Table 4. Cardiovascular Event IRs per 1000 person-years

Transdermal treatment		PY/1000	Events	IR	Unadjusted HR
Composite cardiovascular end point*	Former	139.8	2103	15.04	1.00 (ref)
	Current	36.9	434	11.77	0.78 (0.7–0.87)
	No use	631.2	10108	16.01	1.07 (1.02–1.12)
MI	Former	144.6	1210	8.37	1.00 (ref)
	Current	37.9	246	6.49	0.78 (0.68–0.90)
	No use	651.9	6030	9.25	1.12 (1.05–1.19)
Stroke	Former	148.1	618	4.17	1.00 (ref)
	Current	38.5	131	3.41	0.84 (0.69–1.01)
	No use	666.7	3047	4.57	1.11 (1.02–1.22)
VTE†	Former	148.3	558	3.76	1.00 (ref)
	Current	38.4	106	2.76	0.69 (0.56–0.85)
	No use	670.1	2361	3.52	0.91 (0.83–1.00)
Intramuscular Treatment					
Composite cardiovascular endpoint*	Former	117.8	1902	16.14	1.00 (ref)
	Current	68.9	975	14.15	0.88 (0.82–0.95)
	No use	621.2	9768	15.72	0.98 (0.93–1.03)
MI	Former	121.8	1123	9.22	1.00 (ref)
	Current	70.5	575	8.16	0.90 (0.81–0.99)
	No use	642.2	5788	9.01	0.99 (0.93–1.05)
Stroke	Former	124.9	569	4.56	1.00 (ref)
	Current	72.0	252	3.50	0.80 (0.69–0.93)
	No use	656.4	2975	4.53	1.03 (0.94–1.13)
VTE†	Former	125.4	461	3.68	1.00 (ref)
	Current	71.9	228	3.17	0.83 (0.71–0.97)
	No use	659.4	2336	3.54	0.94 (0.85–1.04)

IR indicates incidence rate; and MI, myocardial infarction.
*Composite cardiovascular end point was composed of MI, ischemic stroke, and VTE.
†VTE: venous thromboembolism, composed of pulmonary embolism and deep vein thrombosis.

as they include noncardiovascular mortality; or angina and transient ischemic attack, as these may be more prone to ascertainment bias than major cardiovascular events such as MI and stroke. In studies of testosterone treatment and risk for separate cardiovascular events, most studies found that testosterone treatment had no overall association with MI[8,13,15,18,24] or was associated with lower MI risk.[17,19] One study reported higher MI risk, but that study may have been biased, as it assumed that clinicians prescribing testosterone would not be influenced if a patient had a recent MI.[5] In studies of testosterone treatment and risk for stroke, testosterone treatment either had no association with stroke[18] or was associated with lower stroke risk.[16,17,19] Finally, in studies of testosterone treatment and VTE risk, most found no overall association with VTE,[7,11,22,23] while one reported higher VTE risk.[31]

The pathophysiologic basis for an association of testosterone treatment with cardiovascular risk is unclear, as testosterone and its metabolites have complex effects on the cardiovascular system.[32–35] Testosterone treatment could increase cardiovascular risk by increased platelet aggregation and hematocrit, which increase viscosity and vascular shear force; increased coronary artery noncalcified plaque volume; exacerbation of severe untreated sleep apnea; or increased levels of estradiol, a metabolite of testosterone, which may induce thrombosis.[32,36–39] In contrast, testosterone treatment could have potential protective effects by a decrease in cardiovascular risk factors such as metabolic syndrome and central obesity; decreased exercise-induced cardiac ischemia; or increased release of endothelial nitric oxide, which causes vasodilation.[33,35,40]

The conflicting results from different studies about the association of testosterone with cardiovascular events may be related to heterogeneity in databases[41] that were used, with some having limited information on medical comorbidities[5,7,8,13,22] and gonadal status.[8,12,13,15,22] Other factors include methodologic issues such as studies[16,23] with immortal time bias[42,43] and other studies with time-dependent confounding attributable to failure to adjust for covariate changes over time.[8,15,16,23] This study avoided these methodologic

Table 5. Cardiovascular Outcomes by Testosterone Treatment Status and Prevalent Cardiovascular Disease

		No prevalent cardiovascular disease*					Prevalent cardiovascular disease*				
Transdermal testosterone		PY/1000	Events	IR	Unadjusted HR	Adjusted HR†	PY/1000	Events	IR	Unadjusted HR	Adjusted HR†
Composite cardiovascular end point‡	Former	71.5	688	9.62	1.00 (ref)	1.00 (ref)	68.3	1415	20.73	1.00 (ref)	1.00 (ref)
	Current	20.7	180	8.68	0.89 (0.75–1.05)	0.89 (0.76–1.05)	16.1	254	15.74	0.74 (0.64–0.84)	0.80 (0.70–0.91)§
	No use	332.2	3424	10.31	1.07 (0.98–1.16)	1.02 (0.94–1.11)	299.0	6684	22.35	1.06 (1–1.12)	1.03 (0.97–1.09)
MI	Former	71.5	359	5.02	1.00 (ref)	1.00 (ref)	73.1	851	11.64	1.00 (ref)	1.00 (ref)
	Current	20.7	95	4.58	0.91 (0.73–1.15)	0.92 (0.73–1.15)	17.2	151	8.78	0.74 (0.62–0.88)	0.80 (0.67–0.95)§
	No use	332.2	1860	5.60	1.12 (1–1.25)	1.06 (0.95–1.19)	319.8	4170	13.04	1.11 (1.03–1.19)	1.07 (0.99–1.15)
Stroke	Former	71.5	168	2.35	1.00 (ref)	1.00 (ref)	76.6	450	5.88	1.00 (ref)	1.00 (ref)
	Current	20.7	45	2.17	0.93 (0.67–1.3)	0.96 (0.69–1.34)	17.7	86	4.85	0.82 (0.65–1.03)	0.90 (0.72–1.14)
	No use	332.2	865	2.60	1.12 (0.95–1.32)	1.06 (0.90–1.25)	334.5	2182	6.52	1.10 (1–1.22)	1.05 (0.94–1.16)
VTE	Former	71.5	172	2.40	1.00 (ref)	1.00 (ref)	76.8	386	5.03	1.00 (ref)	1.00 (ref)
	Current	20.7	42	2.03	0.78 (0.56–1.1)	0.75 (0.53–1.05)	17.6	64	3.63	0.66 (0.5–0.86)	0.72 (0.55–0.94)§
	No use	332.2	739	2.22	0.89 (0.75–1.05)	0.86 (0.73–1.02)	337.9	1622	4.80	0.91 (0.81–1.02)	0.93 (0.83–1.04)
Intramuscular testosterone											
Composite cardiovascular end point‡	Former	59.1	652	11.03	1.00 (ref)	1.00 (ref)	58.7	1250	21.29	1.00 (ref)	1.00 (ref)
	Current	37.8	379	10.03	0.89 (0.79–1.01)	0.91 (0.80–1.04)	31.1	596	19.16	0.88 (0.8–0.98)	0.98 (0.89–1.09)
	No use	327.6	3261	9.96	0.89 (0.81–0.96)	0.82 (0.75–0.89)	293.6	6507	22.16	1.03 (0.97–1.09)	0.96 (0.90–1.02)
MI	Former	59.1	349	5.90	1.00 (ref)	1.00 (ref)	62.7	774	12.34	1.00 (ref)	1.00 (ref)
	Current	37.8	211	5.58	0.93 (0.79–1.11)	0.95 (0.80–1.13)	32.7	364	11.14	0.89 (0.79–1.01)	0.99 (0.87–1.12)
	No use	327.6	1754	5.35	0.89 (0.79–1)	0.84 (0.75–0.94)	314.6	4034	12.82	1.03 (0.95–1.11)	0.97 (0.89–1.04)
Stroke	Former	59.1	158	2.67	1.00 (ref)	1.00 (ref)	65.8	411	6.25	1.00 (ref)	1.00 (ref)
	Current	37.8	90	2.38	0.90 (0.69–1.17)	0.95 (0.73–1.23)	34.2	162	4.73	0.77 (0.64–0.92)	0.87 (0.73–1.05)
	No use	327.6	830	2.53	0.95 (0.8–1.13)	0.86 (0.72–1.02)	328.8	2145	6.52	1.05 (0.95–1.17)	0.94 (0.84–1.04)
VTE	Former	59.1	155	2.62	1.00 (ref)	1.00 (ref)	66.3	306	4.62	1.00 (ref)	1.00 (ref)
	Current	37.8	82	2.17	0.77 (0.59–1.01)	0.77 (0.59–1.00)	34.2	146	4.27	0.87 (0.71–1.06)	0.97 (0.79–1.18)
	No use	327.6	716	2.19	0.79 (0.66–0.94)	0.71 (0.60–0.85)	331.9	1620	4.88	1.02 (0.9–1.15)	0.94 (0.83–1.07)

HR indicates hazard ratio; MI, myocardial infarction; PY, person-years; VTE, venous thromboembolism.

*Cardiovascular disease includes arrhythmia, angina, coronary artery disease, chronic heart failure, cardiomyopathy, peripheral vascular disease, cerebrovascular disease, transient ischemic attack, and cardiovascular procedures. In secondary analyses for separate cardiovascular outcomes, it also included MI, stroke, or VTE except in analyses for that specific outcome.

†Fully adjusted for age, race, geographic region, year of cohort entry, body mass index, hospitalization, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, sexual dysfunction, hyperlipidemia, hypertension, major depression, morbid obesity, polycythemia, sleep apnea, smoking, and cardiovascular disease. Adjustment for the composite end point and VTE also included malignancy (excluding basal cell skin cancer).

‡The composite cardiovascular endpoint was comprised of MI, ischemic stroke, and VTE.

§$p<0.05$.

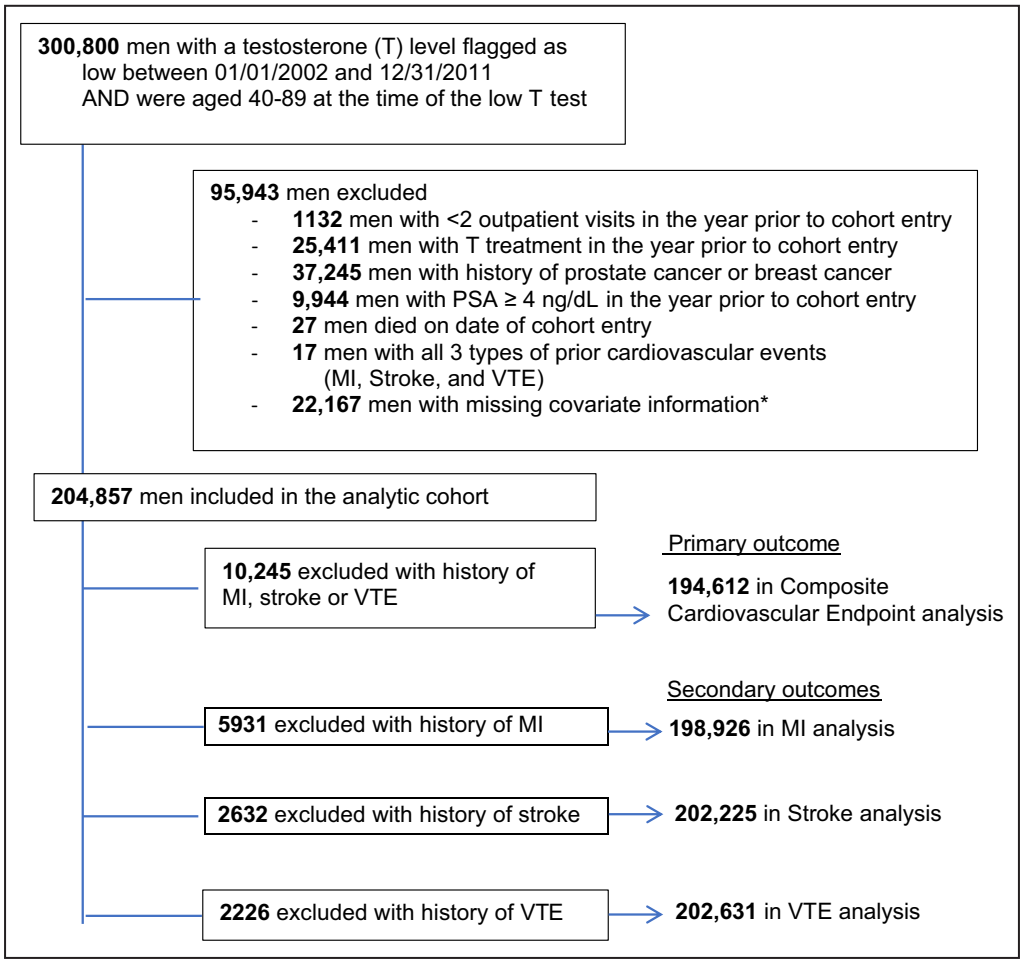

Figure 1. Study cohort inclusions and exclusions.
*Among 22 167 men with missing information: 20 957 were missing information on race, 1200 were missing information on BMI, 825 were missing information on region. These are overlapping groups, as some men were missing >1 covariate. BMI indicates body mass index; MI, myocardial infarction; PSA, prostate-specific antigen; and VTE, venous thromboembolism.

limitations and differed from others in 2 aspects of the analytic approach:

1. *Testosterone exposure*. Several cohort studies modeled testosterone exposure as any use versus no use.[4,8,16,19,23] However, such a model cannot ascertain whether cardiovascular events occurred when subjects were currently treated with testosterone. Furthermore, the any-use /no-use model may lead to an overestimation of testosterone exposure, which could bias results. We modeled testosterone exposure as current use, former use, and no use to more accurately assess the association between current testosterone exposure and cardiovascular events and to account for intermittent treatment. We also modelled testosterone exposure separately by transdermal and intramuscular formulations because of significant differences in pharmacokinetics and serum levels between transdermal and intramuscular formulations.[44,45]
2. *Reference group*. Many cohort studies compared testosterone-treated to -untreated men. However, in cohort studies, untreated subjects are not an ideal reference group, as the treated and untreated groups are likely to differ because of the nonrandomization to treatment.[46] Statistical methods attempt to adjust for this, but there may be residual confounding caused by differences in confounders that are not captured in the data set, such as family history or health habits. For example, studies of hormone replacement therapy in women found that beneficial effects associated with hormone replacement therapy were later found to be attributable to a healthy-user effect in which women on hormone replacement therapy had better health habits, compliance, and medical follow-up than untreated women.[47–49] Thus, to

decrease the risk for confounding, we compared current users of testosterone to former users as both had been selected to initiate testosterone treatment at some point during the study. Another approach is to compare treated men with men treated with a different but comparable medication. However, this approach was not possible, as there is no comparable alternative medication for men with low testosterone.

Limitations

There are several limitations to our study. The study population consisted of US male veterans with multiple medical comorbidities, including a high prevalence of obesity, hypertension, and diabetes mellitus, and these results may not be applicable to healthier men with fewer comorbidities and lower cardiovascular risk. Subjects had 1 low serum testosterone measure, but 2 levels and a clinical assessment are recommended before testosterone treatment.[37,50] We did not have information on manifestations of testosterone deficiency or indications for testosterone treatment and assumed that men started testosterone on the fill date and were compliant with treatment but could not ensure this. Cardiovascular outcomes and medical comorbidities were ascertained with *ICD-9* codes, procedure codes, and laboratory and pharmacy data and not via chart review. We excluded outpatient deep venous thrombosis diagnoses since the accuracy for outpatient deep venous thrombosis diagnoses is low. We did not examine testosterone dosage regimens in our analyses. There were a small number of follow-up serum testosterone levels, as we limited these to current users and nonusers in the first year following cohort entry. The mean follow-up time was short (4.3 years). However, testosterone treatment time itself was short (median cumulative treatment time of 4.8 months for transdermal and 11.1 months for intramuscular testosterone) and in several studies, adverse cardiovascular events occurred within a relatively short time following testosterone treatment.[5,7–11] Our findings should also be interpreted in the context of multiple comparisons undertaken to examine composite (primary analysis) and separate cardiovascular outcomes (secondary analyses), each by testosterone formulation and prevalent cardiovascular disease status. Finally, because of the observational study design, these results do not imply causality, and residual confounding cannot be excluded.

Strengths

Despite these limitations, our study has several strengths. First, we had a large cohort with a high number of testosterone-treated men (82 555) and cardiovascular events, which enhanced our ability to detect a safety signal. In contrast, other studies had a relatively low number of testosterone-treated men and cardiovascular events.[4,11,18,24] We restricted our analyses to men who had no history of the specific cardiovascular outcome to decrease heterogeneity among subjects and reduce the possibility that cardiovascular events were related to recurrent disease, independent of testosterone treatment. Another strength was that VHA diagnoses were supplemented with Centers for Medicare and Medicaid Services diagnoses to capture acute cardiovascular events that were treated in non-VHA settings. Other strengths include a new-user design[51] and detailed models of testosterone exposure that allowed us to characterize treatment status by formulation and distinguish current treatment from former treatment. In contrast, many cohort studies used an any-use/no-use model of testosterone treatment and were unable to ascertain if cardiovascular events occurred when subjects were currently treated with testosterone.[4,8,12,16,19,23,24] Finally, we attempted to minimize the risk for confounding by using former users (rather than nonusers) as the reference group and continuously adjusted for changes in medical covariates to adjust for differences between groups. Another approach to adjust for differences between groups is propensity score analysis, but this approach does not offer advantages in studies that have a large number of subjects and events.[52]

CONCLUSIONS

In a large cohort of US male veterans, aged ≥40 years, with low testosterone and multiple medical comorbidities, we did not detect increased risk for composite or separate cardiovascular events of MI, stroke, or VTE with current use compared with former use of transdermal or intramuscular testosterone. Given the large study size and detailed characterization of testosterone exposure, this study provides some reassurance that testosterone treatment does not appear to pose a significant risk for major cardiovascular events of MI, stroke, or thrombosis. However, a large, carefully designed prospective, randomized, double-blind, placebo-controlled trial is needed to definitively assess the cardiovascular risks associated with testosterone treatment. Until such a trial is completed, clinicians should follow recommended guidelines regarding testosterone treatment and carefully review potential risks and benefits of treatment in men who have unequivocal hypogonadism.[37,50]

ARTICLE INFORMATION

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Supplementary Material

Data S1
Tables S1–S5
References 4, 9, 12, 14, 18,19, 25

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Supplemental Material

Data S1. Case-crossover design comparing current and former testosterone treatment among those with a composite cardiovascular outcome.

In this study design, subjects with a composite cardiovascular outcome serve as their own control at the selected times prior to the cardiovascular outcome. Testosterone treatment status (current or former) was determined at the time of the cardiovascular outcome and at 1, 3, and 6 months prior to the outcome. This design controls for non-time dependent factors including unmeasured in-person confounders. In this exploratory analysis, we did not consider further adjustments and our investigation was limited to those who had treatment during follow-up (to reduce the possibility of treatment bias) and who were either on current treatment or former treatment at the time prior to and at the time of the outcome. In addition, both modalities of treatment (intramuscular and transdermal) were combined into a single testosterone exposure.

The three tables below present the windows of testosterone treatment 1, 3, and 6 months prior to the composite cardiovascular outcome as the control. The table diagonals (former & former treatment and current & current treatment) contain the majority of the subjects, indicating that treatment status is relatively stable across the follow-up periods. These cells do not inform the analysis, as the subject is on the same treatment prior to the event and at the event. The subjects with *discordant* treatment status inform the case-crossover analysis: the case-crossover odds ratio is estimated by the ratio of the counts in the cells with discordant treatment status. For each control time period (1, 3, and 6 months), the estimated odds ratio (OR) was consistent with an association towards protection by current treatment rather than harm. The proportion of those on current treatment is lower at the time of the composite outcome than at control time prior to the composite outcome. McNemar's test was used to test the null hypothesis of no association.

Table 1. Testosterone treatment one month prior to composite outcome vs testosterone treatment at time of the composite outcome

		Testosterone treatment 1 month prior to outcome		
		Current	Former	Total
Testosterone treatment at outcome	Current	1023	293	1316
	Former	309	3203	3512
	Total	1332	3469	4828

Proportion of subjects on current treatment at time of composite outcome: 0.273
Proportion of subjects on Current treatment one month prior to composite outcome: 0.276
OR = 0.95 (95% CI: 0.81-1.12); p-value=0.51

Table 2. Testosterone treatment three months prior to composite outcome vs testosterone treatment at time of the composite outcome

		Testosterone treatment 3 months prior to outcome		
		Current	Former	Total
Testosterone treatment at outcome	Current	935	351	1286
	Former	475	3010	3485
	Total	1410	3361	4771

Proportion of subjects on current treatment at time of composite outcome: 0.270
Proportion of subjects on current treatment three months prior to composite outcome: 0.296
OR = 0.74 (95% CI: 0.64-0.85); p-value <0.01

Table 3. Testosterone treatment six months prior to composite outcome vs testosterone treatment at composite outcome

		Testosterone treatment 6 months prior to outcome		
		Current	Former	Total
Testosterone treatment at outcome	Current	836	371	1207
	Former	562	2839	3401
	Total	1398	3210	4608

Proportion of subjects on current treatment at time of composite outcome: 0.262
Proportion of subjects on current treatment six months prior to composite outcome: 0.303
OR = 0.66 (95% CI: 0.58-0.75); p-value <0.01

Table S1. Criteria for Cardiovascular Outcomes

Cardiovascular Events	ICD-9 Diagnostic Codes	ICD-9 Procedure Code	CPT4[#]	Internal Entry Number (IEN)*
Myocardial infarction	410.0, 410.00-410.02, 410.1, 410.10-410.12, 410.2, 410.20-410.22, 410.3, 410.30-410.32, 410.4, 410.40-410.42, 410.5, 410.50-410.52, 410.6, 410.60-410.62, 410.7, 410.70-410.72, 410.8, 410.80-410.82, 410.9, 410.90-410.92			
Pulmonary embolism	415.1, 415.11, 415.13, 415.19			
Deep vein thrombosis (DVT)[^]	451.1, 451.11,451.19, 451.2, 451.8, 451.81-451.84, 451.89, 451.9, 453.0, 453.1, 453.2, 453.40-453.42, 453.8, 453.81-453.87, 453.89, 453.9	38.7	75940, 75941	11785, 12935, 12938, 13678, 15894, 17111, 18874, 18877, 21208, 21213, 21214, 21215, 22021, 22022, 22575, 22765, 4653, 4654, 4658, 4660, 12362, 12932, 13675, 13676, 15440, 15895, 15896, 17183, 18878, 21207, 21209, 21210, 21212, 22573, 22764, 22766, 4652, 4656, 11784, 11787, 12936, 13624, 13625, 13674, 13677, 13679, 15439, 17110, 17112, 18876, 19109, 21211, 22019, 22020, 4650, 4651, 4657, 4659, 11783, 11786, 12360, 12361, 12933, 12934, 14609, 15480, 22763, 4655, 5592, 5593
Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436			

[#]CPT: Current procedural terminology procedure code

[*]IEN (internal entry number) for VHA pharmacy data for anticoagulants.

[^] Criteria for DVT required both an ICD-9 diagnostic code and either inferior vena cava filter placement or anticoagulation treatment

Table S2. Covariate Codes

Characteristic	Based on	Codes
Cardiac Arrhythmia	ICD-9 codes	ICD-9 codes: 426.xx, 427.xx
Cardiomyopathy	ICD-9 codes	ICD-9 codes: 425.xx
Cerebrovascular Disease	ICD-9 codes	ICD-9 codes: 38.11, 430.x, 431.x, 434.x, 435.x, 436; 437, 437.0, 437.1, 437.8, 437.9, V12.54
Chronic Heart Failure	ICD-9 codes	ICD-9 codes: 428.xx, 398.91
Chronic Kidney Disease	ICD-9 codes or LOINC[#] for GFR* $\leq$ 45	ICD-9 codes: 585, 585.3x, 585.4x, 585.5x, 585.6x, 585.9x LOINCs: 62238-1, 33914-3, 48642-3, 48643-1, 70969-1, 50384-7
Chronic Liver Failure	ICD-9 codes	ICD-9 codes: 456.0, 456.1, 456.2x, 571.2, 571.3, 571.40, 571.41, 571.42, 571.49, 571.5, 571.6, 571.8, 571.9, 572.2, 572.3, 572.4, 572.8
COPD[~]	ICD-9 codes	ICD-9 codes: 491.2x, 492.xx, 493.xx, 496.xx
Coronary artery disease and angina	ICD-9 codes or CPT[$] codes	ICD-9 codes: 411.1, 411.8, 411.81, 411.89, 412.xx, 414.4, 414.8, 414.9; 413.0, 413.1, 413.9 ICD-9 procedure codes: 36.0-36.17, 36.19, 36.2 CPT codes: 33510-14, 33516- 33523, 33525, 33528, 92980- 92982, 92984
Diabetes	ICD-9 codes or IEN[&] for insulin and oral hypoglycemics or LOINC for $HbA_1C > 6$	ICD-9 codes: 250.xx, 362.0x IEN: 22955, 17238, 17239, 14371, 14913, 16264, 16280, 17587, 18029, 19354, 20717, 822, 826, 829, 831, 834, 838, 841, 845, 846, 850, 852, 858, 862, 863, 868, 873, 874, 879, 880, 886, 888, 889, 891, 13113, 13485, 16265, 16466, 16467, 16746, 17588, 18242, 18243, 18690, 823, 824, 828, 836, 837, 842, 844, 853, 856, 867, 869, 871, 875, 882, 885, 890, 13351, 13484, 14591, 14592, 16199, 16200, 16437, 16665, 17851, 18590, 19355, 825, 827, 839, 840, 851, 854, 855, 857, 859, 860, 864, 866, 870, 877, 881, 883, 884, 887, 13352, 13353, 13486, 14476, 14477, 16263, 16370, 17849, 17850, 17894, 19356, 20714, 821, 830, 832, 833, 835, 843, 847, 848, 849, 861, 865, 872, 876, 878, 892, 12469, 12485, 13579, 14537, 15347, 15983, 16137, 17220, 1780, 18086, 18282, 1836, 19238, 2079, 21861, 22043, 22947, 23321, 23629, 23631, 23632, 23638, 23797, 4519, 12369, 12470, 12472, 12483, 12484, 12594, 12766, 13507, 13508, 13580, 13581, 13712, 13713, 13714, 14538, 14620, 15981, 15982, 16125, 16139, 17926, 18281, 1837, 19239, 2078, 20859, 22946, 22948, 22959, 23796, 2877, 576, 12468, 12471, 12592, 12593, 12768, 12901, 12976, 13875, 14539, 14941, 16635, 16711, 1779, 1781, 1782, 17912, 18006, 18009, 20177, 21862, 22042, 22389, 22732, 22733, 22958, 22960, 23333, 23623, 23624, 23630, 23637, 2876, 2879, 2880, 4518, 4520, 4521, 12370, 12767, 12899, 12900, 13509, 14319, 14940, 16124, 16126, 16138, 17191, 17542, 17543, 17925, 17927, 18007, 18008, 18010, 18011, 18085, 19240, 20559, 20561, 20858, 22041, 22731, 23332, 23622, 23628, 23633, 2878, 2881, 577, 21531, 17188, 19123, 19375, 19124, 19125 LOINCs: 41995-2, 55454-3, 4548-4, 4549-2, 17855-8, 17856-6, 59261-8, 71875-9, 62388-4
Sexual Dysfunction	ICD-9 codes or	ICD-9 codes: 302.70, 302.71, 302.72, 302.74, 302.75, 302.76, 607.84, 799.81

Sexual Dysfunction (con)	IENs for medications for erectile dysfunction	IENs: 16380, 16384, 12823, 16381, 16385, 16522, 20312, 22644, 12822, 12824, 16520, 16521, 16379, 16382, 16383, 16146, 2956, IENs: 2957, 2962, 2963, 2954, 2961, 2964, 16147, 16509, 2955, 2965, 16148, 16508, 2958, 2959, 2960, 2966
Hyperlipidemia	ICD-9 codes or IENs for lipid-lowering medications	ICD-9 codes: 272.0x, 272.1x, 272.2x IENs: 13591, 18377, 22009, 5850, 5851, 5854, 5856, 5859, 5861, 5862, 5864, 6227, 13589, 18376, 18378, 21539, 22008, 22010, 5846, 5853, 5860, 6223, 13592, 17507, 21541, 5847, 5855, 5857, 5858, 6226, 13588, 13590, 21540, 5848, 5849, 5852, 5863, 6224, 6225, 11937, 12860, 12861, 13578, 14096, 14585, 14760, 15318, 15470, 15866, 16386, 16389, 16400, 16403, 16531, 16775, 16776, 16880, 17012, 17338, 17552, 18969, 19385, 21013, 23564, 2907, 5098, 5238, 6115, 6116, 6118, 7994, 12596, 14759, 15317, 15865, 16004, 16390, 16392, 16405, 16442, 16532, 16877, 16879, 16882, 16883, 16885, 17013, 17335, 17336, 19374, 19386, 19387, 19510, 19636, 20339, 21312, 21729, 23572, 23859, 23860, 2906, 2908, 2909, 6114, 6119, 8519, 9680, 9741, 12595, 12597, 13788, 14321, 14618, 16135, 16244, 16387, 16391, 16404, 16881, 16884, 18040, 19527, 20340, 21014, 21310, 21311, 21867, 23735, 23858, 2910, 5239, 6117, 8520, 9743, 9744, 11938, 12831, 12914, 13725, 14527, 14594, 14960, 15864, 16003, 16388, 16401, 16402, 16530, 16777, 16878, 17334, 17337, 18970, 19366, 19526, 19637, 21509, 21866, 23563, 23565, 23864, 4436, 5097, 6113, 8521, 9681, 9682, 9742
Hypertension	ICD-9 codes	ICD-9 codes: 401.xx, 402.xx, 403.xx, 404.xx, 405.xx
Major Depression	ICD-9 codes	ICD-9 codes: 296.2x-296.3x
Malignancy	ICD-9 codes	ICD-9 codes: 140.xx-239.xx (except excluded basal cell cancer: 173.xx)
Morbid Obesity	ICD-9 codes	ICD-9 codes: V85.4x, 278.01
Peripheral Vascular Disease	ICD-9 codes or CPT codes	ICD-9 codes: 38.18, 38.19, 38.38, 38.39, 38.48, 38.49, 38.88, 38.89, 39.25, 39.26, 39.28, 39.29, 39.50, 39.90, 433, 433.9, 440.2x, 440.3x, 440.4x, 442.x, 443.x, 445.0x CPT codes: 34800, 34802, 34803, 34804, 34805, 35226, 35256, 35286, 35351, 35355, 35371, 35372, 35381, 35454, 35456, 35459, 35473, 35474, 35482, 35483, 35485, 35492, 35493, 35495, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35583, 35585, 35587, 35646, 35656, 35661, 35663, 35665, 35666, 35671
Polycythemia	ICD-9 codes or LOINCs for Hematocrit $\geq$52	ICD-9 codes: 289.0x LOINCs: 24360-0, 4544-3, 71833-8, 4545-0, 48703-3, 20570-8, 41655-2, 71830-4, 31100-1
PSA^{+}	LOINC laboratory codes	LOINCs: 19195-7, 19197-3, 2857-1, 35741-8, 10886-0, 19201-3, 19203-9, 12841-3, 14120-0, 33667-7, 15323-9, 15324-7, 15325-4
Sleep Apnea	ICD-9 codes or CPT codes for CPAP$^{\wedge}$	ICD-9 codes: 780.51, 780.53, 780.57 CPT codes: E0452, E0601, 94660
Smoking	ICD-9 codes or IEN codes for smoking cessation medications	ICD-9 codes: V15.82, 305.1x, 989.84 IENs: 17847, 23100, 9697, 9703, 16376, 18746, 18749, 22944, 5095, 9700, 9701, 16375, 17845, 18747, 5096, 9696, 13203, 16685, 17846, 17848, 18748, 22943, 9694, 9695, 9698, 9699, 9702

Testosterone Formulations	IEN for testosterone medications	IENs: 513, 514, 515, 516, 518, 524, 525, 526, 527, 530, 531, 532, 533, 534, 14379, 14380, 14775, 15507, 15508, 16064, 16544, 17475, 17503, 17901, 21468, 21470, 21471, 22219, 22384, 22523, 22526, 22791, 168, 169, 170, 171, 172, 173, 174, 512, 517, 519, 520, 521, 522, 523, 528, 529, 1301, 1302, 1303, 3055, 3637, 3638, 3639, 3795, 4220, 4550, 4551, 4552, 4553, 4554, 4555, 4556, 6577, 6578, 6976, 16141
Testosterone Level	LOINC for serum testosterone measures	LOINCs: 14913-8, 1639-4, 21555-8, 2986-8, 49041-7, 49042-7, 55519-3, 58835-0, 70239-9, 51005-7, 58716-2, 49042-5, 49043-3, 70240-7, 58952-3, 2990-0, 30123-4, 14914-6, 25987-9, 2991-8, 35225-2, 24125-7, 15432-8, 16286-7, 17686-7

~COPD: Chronic obstructive pulmonary disease

^CPAP: Continuous positive airway pressure

$CPT: Current procedural terminology procedure code

*GFR: Glomerular filtration rate

&IEN: Internal Entry Numbers for medications,

#LOINC: Logical observation identifiers names and codes for laboratory data

+PSA: Prostate specific antigen

Table S3. Results using different definitions for current testosterone treatment

		Adjusted HR (No Prevalent CVD at cohort entry)						
TD Treatment		No overrun	10%	20%*	25%	30%	35%	40%
Composite Cardiovascular Endpoint#	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.89 (0.74-1.05)	0.87 (0.74-1.03)	0.89 (0.76-1.05)	0.88 (0.75-1.04)	0.88 (0.75-1.04)	0.89 (0.76-1.05)	0.90 (0.77-1.05)
	No use	1.02 (0.94-1.11)	1.01 (0.93-1.1)	1.02 (0.94-1.11)	1.02 (0.93-1.10)	1.02 (0.93-1.10)	1.02 (0.93-1.11)	1.02 (0.94-1.11)
MI	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.91 (0.72-1.16)	0.88 (0.7-1.11)	0.92 (0.73-1.15)	0.90 (0.72-1.13)	0.90 (0.72-1.12)	0.90 (0.72-1.13)	0.88 (0.70-1.10)
	No use	1.07 (0.95-1.19)	1.06 (0.94-1.18)	1.06 (0.95-1.19)	1.06 (0.95-1.19)	1.06 (0.94-1.19)	1.06 (0.94-1.19)	1.05 (0.94-1.18)
Stroke	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	1 (0.71-1.41)	0.98 (0.7-1.37)	0.96 (0.69-1.34)	0.93 (0.67-1.29)	0.91 (0.65-1.27)	0.89 (0.64-1.24)	0.91 (0.66-1.26)
	No use	1.07 (0.91-1.26)	1.06 (0.9-1.26)	1.06 (0.90-1.25)	1.05 (0.89-1.24)	1.05 (0.89-1.24)	1.04 (0.88-1.23)	1.05 (0.88-1.24)
VTE	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.7 (0.49-1.01)	0.73 (0.52-1.04)	0.75 (0.53-1.05)	0.77 (0.55-1.07)	0.80 (0.57-1.11)	0.82 (0.60-1.14)	0.89 (0.65-1.21)
	No use	0.86 (0.72-1.01)	0.86 (0.73-1.01)	0.86 (0.73-1.02)	0.87 (0.73-1.03)	0.87 (0.73-1.03)	0.88 (0.74-1.04)	0.89 (0.75-1.06)
IM Treatment								
Composite Cardiovascular Endpoint#	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.91 (0.8-1.04)	0.91 (0.8-1.04)	0.91 (0.80-1.04)	0.89 (0.79-1.01)	0.89 (0.79-1.01)	0.90 (0.79-1.02)	0.90 (0.80-1.02)
	No use	0.82 (0.76-0.89)	0.82 (0.76-0.89)	0.82 (0.75-0.89)	0.81 (0.75-0.89)	0.81 (0.75-0.89)	0.81 (0.75-0.89)	0.81 (0.75-0.89)
MI	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.93 (0.78-1.1)	0.95 (0.8-1.13)	0.95 (0.80-1.13)	0.93 (0.78-1.10)	0.93 (0.79-1.11)	0.95 (0.80-1.12)	0.95 (0.81-1.13)
	No use	0.83 (0.74-0.93)	0.84 (0.75-0.94)	0.84 (0.75-0.94)	0.83 (0.74-0.93)	0.83 (0.74-0.93)	0.83 (0.74-0.94)	0.84 (0.74-0.94)
Stroke	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.97 (0.75-1.27)	0.95 (0.73-1.23)	0.95 (0.73-1.23)	0.92 (0.71-1.19)	0.94 (0.73-1.22)	0.95 (0.74-1.23)	0.93 (0.72-1.20)
	No use	0.87 (0.73-1.03)	0.86 (0.73-1.02)	0.86 (0.72-1.02)	0.85 (0.72-1.01)	0.86 (0.72-1.02)	0.86 (0.72-1.03)	0.85 (0.72-1.02)
VTE	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.8 (0.61-1.05)	0.78 (0.59-1.02)	0.77 (0.59-1.00)	0.76 (0.58-1.00)	0.74 (0.57-0.97)	0.74 (0.56-0.96)	0.75 (0.57-0.98)
	No use	0.73 (0.61-0.87)	0.72 (0.6-0.86)	0.71 (0.60-0.85)	0.71 (0.60-0.85)	0.70 (0.59-0.84)	0.70 (0.59-0.84)	0.70 (0.59-0.84)

		Adjusted HR (Prevalent CVD at cohort entry)						
TD Treatment		No overrun	10%	20%*	25%	30%	35%	40%
Composite Cardiovascular Endpoint[#]	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.81 (0.7-0.93)	0.81 (0.7-0.92)	0.80 (0.70-0.91)	0.83 (0.73-0.95)	0.84 (0.73-0.95)	0.85 (0.75-0.96)	0.87 (0.77-0.99)
	No use	1.04 (0.98-1.1)	1.03 (0.97-1.09)	1.03 (0.97-1.09)	1.03 (0.97-1.1)	1.04 (0.98-1.1)	1.04 (0.98-1.1)	1.04 (0.98-1.11)
MI	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.81 (0.67-0.97)	0.83 (0.69-0.99)	0.80 (0.67-0.95)	0.8 (0.68-0.96)	0.81 (0.69-0.96)	0.82 (0.69-0.97)	0.84 (0.71-0.99)
	No use	1.07 (1-1.16)	1.07 (1-1.16)	1.07 (0.99-1.15)	1.07 (0.99-1.15)	1.07 (0.99-1.15)	1.07 (0.99-1.16)	1.07 (1-1.16)
Stroke	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.92 (0.72-1.17)	0.9 (0.71-1.14)	0.90 (0.72-1.14)	0.94 (0.75-1.18)	0.94 (0.75-1.18)	0.97 (0.78-1.21)	0.99 (0.8-1.23)
	No use	1.05 (0.95-1.17)	1.05 (0.95-1.16)	1.05 (0.94-1.16)	1.06 (0.95-1.17)	1.05 (0.95-1.17)	1.06 (0.95-1.18)	1.07 (0.96-1.18)
VTE	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.73 (0.55-0.96)	0.7 (0.53-0.92)	0.72 (0.55-0.94)	0.75 (0.58-0.98)	0.78 (0.6-1)	0.78 (0.6-1)	0.82 (0.64-1.05)
	No use	0.93 (0.83-1.04)	0.93 (0.83-1.04)	0.93 (0.83-1.04)	0.93 (0.83-1.04)	0.94 (0.83-1.05)	0.93 (0.83-1.05)	0.94 (0.84-1.06)
IM Treatment								
Composite Cardiovascular Endpoint[#]	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.99 (0.9-1.1)	0.99 (0.9-1.09)	0.98 (0.89-1.09)	0.97 (0.88-1.07)	0.97 (0.88-1.07)	0.97 (0.88-1.06)	0.97 (0.88-1.06)
	No use	0.96 (0.9-1.02)	0.96 (0.9-1.02)	0.96 (0.90-1.02)	0.95 (0.89-1.01)	0.95 (0.89-1.01)	0.95 (0.89-1.01)	0.95 (0.89-1.01)
MI	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.99 (0.87-1.13)	1 (0.88-1.13)	0.99 (0.87-1.12)	0.97 (0.86-1.1)	0.97 (0.85-1.09)	0.97 (0.85-1.09)	0.97 (0.86-1.1)
	No use	0.96 (0.89-1.04)	0.97 (0.89-1.05)	0.97 (0.89-1.04)	0.96 (0.88-1.04)	0.96 (0.88-1.04)	0.96 (0.88-1.04)	0.96 (0.88-1.04)
Stroke	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.89 (0.74-1.08)	0.89 (0.74-1.07)	0.87 (0.73-1.05)	0.86 (0.72-1.04)	0.9 (0.75-1.07)	0.91 (0.76-1.08)	0.9 (0.75-1.07)
	No use	0.95 (0.85-1.05)	0.94 (0.85-1.05)	0.94 (0.84-1.04)	0.93 (0.83-1.04)	0.94 (0.84-1.05)	0.94 (0.84-1.05)	0.94 (0.84-1.05)
VTE	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.96 (0.78-1.18)	0.96 (0.78-1.17)	0.97 (0.79-1.18)	0.96 (0.79-1.17)	0.96 (0.79-1.17)	0.94 (0.78-1.15)	0.97 (0.8-1.18)
	No use	0.94 (0.83-1.07)	0.94 (0.83-1.07)	0.94 (0.83-1.07)	0.94 (0.83-1.07)	0.94 (0.83-1.07)	0.93 (0.82-1.06)	0.94 (0.83-1.07)

Results using different definitions for current testosterone treatment with an overrun ranging from none to 40% of prescription duration. Current testosterone is defined as prescription duration plus a 20% overrun. An overrun was included to account for refill times, noncompliance or residual effects. This sensitivity analysis varies the overrun from 0-40%.

* 20% overrun is the definition for current testosterone treatment that is used in the paper.

[#]The composite cardiovascular endpoint was comprised of MI, stroke and VTE.

Table S4. Incidence rates (IR) associated with testosterone initiation during continuous treatment with testosterone[#]

MI	Continuous treatment time	PY/1000	Events	IR (95% CI)
TD*	-All continuous treatment time	8.5	64	7.51 (5.87-9.59)
	-1st Year continuous treatment	8.4	64	7.65 (5.99-9.78)
	- 6 Months continuous treatment	7.8	63	8.03 (6.28-10.29)
	- 3 Months continuous treatment	6.6	52	7.92 (6.03-10.40)
IM[+]	- All continuous treatment time	13.1	113	8.62 (7.17-10.37)
	-1st Year continuous treatment	12.0	101	8.41 (6.92-10.22)
	- 6 Months continuous treatment	10.0	87	8.71 (7.06-10.75)
	- 3 Months	7.0	61	8.69 (6.76-11.17)

* IR = 6.49 for current-use of TD in the primary analysis;
[+] IR = 8.16 for current-use of IM in the primary analysis

STROKE	Continuous treatment time	PY/1000	Events	IR (95% CI)
TD[$]	- All continuous treatment time	8.6	34	3.93 (2.81-5.50)
	-1 Year continuous treatment	8.5	34	4.01 (2.86-5.61)
	- 6 Months continuous treatment	8.0	31	3.90 (2.74-5.54)
	-3 Months continuous treatment	6.7	26	3.90 (2.66-5.73)
IM[&]	-All continuous treatment time	13.3	34	2.55 (1.82-3.57)
	-1 Year continuous treatment	12.2	34	2.78 (1.99-3.89)
	- 6 Months continuous treatment	10.2	26	2.56 (1.74-3.76)
	-3 Months continuous treatment	7.1	19	2.66 (1.70-4.17)

[$] IR = 3.41 for current-use of TD in the primary analysis,
[&] IR = 3.50 for current-use of IM in the primary analysis

VTE	Continuous treatment time	PY/1000	Events	IR (95% CI)
TD[~]	-All continuous treatment time	8.6	28	3.24 (2.24-4.69)
	-1 Year continuous treatment	8.5	28	3.30 (2.28-4.78)
	- 6 Months continuous treatment	8.0	28	3.52 (2.43-5.10)
	-3 Months continuous treatment	6.7	26	3.90 (2.66-5.73)
IM[^]	All Continuous treatment time	13.3	39	2.92 (2.14-4.00)
	-1 Year continuous treatment	12.2	37	3.03 (2.19-4.18)
	- 6 Months continuous treatment	10.2	35	3.44 (2.47-4.80)
	-3 Months continuous treatment	7.1	20	2.80 (1.81-4.34)

[~] IR = 2.76 for current-use of TD in the primary analysis
[^]IR = 3.17 for current-use of IM in the primary analysis

[#]Incidence rates were those associated with testosterone initiation during continuous monotherapy treatment with testosterone. Subjects were censored at the end of the initial period of continuous testosterone treatment or if they switched to a different testosterone formulation.

Table S5. Criteria for Composite Cardiovascular Endpoint in Different Studies

	MI[&]	VTE[+]	Stroke	TIA[^]	Unstable angina	Re-Vascularization Procedures	SCD[#]	Total mortality
Vigen[4]	x		Ischemic					x
Anderson[18]	x		Ischemic & hemorrhagic					x
Wallis[12]	x	x	Ischemic					
Layton[9]	x		Ischemic	x	x			
Cheetham[19]	x		Ischemic	x	x	x	x	
Argalious[25]	x	x	Ischemic & hemorrhagic					x*
Loo[14]	x		Ischemic	x				

[&]MI: myocardial infarction
*Mortality defined as post-operative, in-hospital mortality
[#]SCD: sudden cardiac death
[^]TIA: transient ischemic attack
[+]VTE: venous thromboembolism consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE)