

# Association of Testosterone Replacement With Cardiovascular Outcomes Among Men With Androgen Deficiency

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**IMPORTANCE** Controversy exists regarding the safety of testosterone replacement therapy (TRT) following recent reports of an increased risk of adverse cardiovascular events.

**OBJECTIVE** To investigate the association between TRT and cardiovascular outcomes in men with androgen deficiency.

**DESIGN, SETTING, AND PARTICIPANTS** A retrospective cohort study was conducted within an integrated health care delivery system. Men at least 40 years old with evidence of androgen deficiency either by a coded diagnosis and/or a morning serum total testosterone level of less than 300 ng/dL were included. The eligibility window was January 1, 1999, to December 31, 2010, with follow-up through December 31, 2012.

**EXPOSURES** Any prescribed TRT given by injection, orally, or topically.

**MAIN OUTCOMES AND MEASURES** The primary outcome was a composite of cardiovascular end points that included acute myocardial infarction (AMI), coronary revascularization, unstable angina, stroke, transient ischemic attack (TIA), and sudden cardiac death (SCD). Multivariable Cox proportional hazards models were used to investigate the association between TRT and cardiovascular outcomes. An inverse probability of treatment weight, propensity score methodology, was used to balance baseline characteristics.

**RESULTS** The cohorts consisted of 8808 men (19.8%) ever dispensed testosterone (ever-TRT) (mean age, 58.4 years; 1.4% with prior cardiovascular events) and 35 527 men (80.2%) never dispensed testosterone (never-TRT) (mean age, 59.8 years; 2.0% with prior cardiovascular events). Median follow was 3.2 years (interquartile range [IQR], 1.7-6.6 years) in the never-TRT group vs 4.2 (IQR, 2.1-7.8) years in the ever-TRT group. The rates of the composite cardiovascular end point were 23.9 vs 16.9 per 1000 person-years in the never-TRT and ever-TRT groups, respectively. The adjusted hazard ratio (HR) for the composite cardiovascular end point in the ever-TRT group was 0.67 (95% CI, 0.62-0.73). Similar results were seen when the outcome was restricted to combined stroke events (stroke and TIA) (HR, 0.72; 95% CI, 0.62-0.84) and combined cardiac events (AMI, SCD, unstable angina, revascularization procedures) (HR, 0.66; 95% CI, 0.60-0.72).

**CONCLUSIONS AND RELEVANCE** Among men with androgen deficiency, dispensed testosterone prescriptions were associated with a lower risk of cardiovascular outcomes over a median follow-up of 3.4 years.

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Starting at age 30 years, testosterone levels decline by an average of 3.1 to 3.5 ng/dL per year (to convert testosterone to nanomoles per liter, multiply by 0.0347).<sup>1,2</sup> Hypogonadal testosterone levels are seen in 19% of men in their 60s, 28% of men in their 70s, and 49% of men in their 80s (using a value of <325 ng/dL to define hypogonadal level).<sup>1</sup> In general, these declines are not associated with symptomatology, although in some men, symptoms of androgen deficiency are pronounced. Symptoms of androgen deficiency include loss of sexual desire, erectile dysfunction, breast enlargement or tenderness, hot flashes, reduced energy (ie, weakness, fatigue, malaise), irritability, and depressed mood. However, many men with these symptoms do not have documented low testosterone levels.<sup>3</sup> The Endocrine Society therefore defines androgen deficiency as consistently low serum testosterone levels (morning levels measured on >1 occasion) in combination with 1 or more androgen deficiency symptom.<sup>3</sup>

Androgen deficiency can be treated with exogenously administered testosterone, resulting in improvement in symptoms of fatigue, muscle strength, body mass index, and mood.<sup>3,4</sup> Recently concern has been raised about testosterone replacement therapy (TRT) owing to reports of adverse cardiovascular (CV) events.<sup>5-7</sup> However, not all studies have found an association between TRT and an increased risk of death or CV outcomes.<sup>8,9</sup> In addition, there is a body of evidence that suggests low serum testosterone levels in older men are associated with increased CV risk and that TRT may have CV benefits.<sup>10-12</sup>

Patient selection may have played a role in the findings from studies showing an increased CV risk with TRT; Vigen et al<sup>6</sup> selected patients with low serum testosterone but a high CV burden, and Finkle et al<sup>7</sup> included patients based on receipt of a new testosterone prescription without regard to an androgen deficiency indication or low testosterone levels. To address this issue, we studied TRT in men likely to have androgen deficiency based on diagnoses or documented low serum testosterone levels and assessed the association between TRT and CV outcomes.

## Methods

### Design

This was a retrospective cohort study in men 40 years or older with documentation of androgen deficiency at Kaiser Permanente California. The primary comparison was between patients dispensed a new testosterone prescription and similar individuals not dispensed TRT.

### Setting

The study was conducted at 2 Kaiser Permanente (KP) regions in California, KP Northern California and KP Southern California. Combined, these 2 KP regions have a current membership of more than 7.8 million individuals. The demographic profile of the KP membership is diverse and closely resembles the underlying population of Northern and Southern California.<sup>13</sup>

Most medical care is provided through KP facilities, which includes 35 hospitals (14 KP Southern California and 21 KP

## Key Points

**Question** What are the cardiovascular risks of testosterone replacement therapy (TRT) in men with androgen deficiency?

**Findings** When use in androgen-deficient men with documented low morning testosterone levels, TRT was not associated with an increased risk of cardiovascular outcomes. During long-term follow-up the risk of cardiovascular outcomes was lower in testosterone-treated men.

**Meaning** These findings support the use of TRT in androgen-deficient men.

Northern California hospitals) and approximately 445 outpatient clinics (200 KP Southern California and 245 KP Northern California clinics). Beginning in 2006, all aspects of care and patient interactions with the health care delivery system are captured in an electronic medical record (EMR). The data generated through the EMR are available for research purposes and include information on membership and benefits, demographic characteristics, dispensed prescriptions, coded diagnoses and procedures, and laboratory test results. Data prior to 2006 are contained in a comprehensive research data warehouse that exists in each region. In addition, covered care delivered in non-KP settings is captured by a claims reimbursement system (ie, emergency department care). The study was approved by the institutional review board at KP Southern and KP Northern California; the institutional review boards waived the requirement for written informed consent.

### Patients

To be included in the study, men had to have evidence of androgen deficiency either by a coded diagnosis in their medical record or by serum testosterone laboratory testing. The following criteria were used to define hypogonadism: (1) *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis codes commonly used within KP to specify androgen deficiency (257.2, 257.8, and 257.9) and/or (2) serum total testosterone levels of less than 300 ng/dL.

Male patients meeting the androgen-deficiency criteria between January 1, 1999, and December 31, 2010, were eligible for inclusion in the study cohort; the cohort was then followed through December 31, 2012. Within this time window, the date of cohort entry was the first date indicating androgen deficiency, either the first diagnosis date or the date of the first low testosterone level. Patients were then classified into ever-TRT or never-TRT groups based on their receipt of a dispensed testosterone prescription following the index date. The analysis was restricted to incident TRT by excluding those given testosterone prescription(s) prior to their index date. Eligible men also needed to have 12 months of continuous membership with drug benefit prior to cohort entry and to be 40 years or older at index. Patients were excluded if they had testicular or prostate cancer, pituitary gland disorders, androgen insensitivity syndrome or Klinefelter syndrome. Patients were followed until they reached a study end point, disenrolled from the health plan, death, or the end of study (December 31, 2012).

## Testosterone Exposure

Two sources were used to capture testosterone usage by eligible men. First, dispensed testosterone prescriptions were collected from the KP electronic pharmacy records, and second, data were collected for injectable testosterone (cypionate and enanthate) administered in the medical office and documented in the EMR. The comprehensive research data warehouse has electronic pharmacy records going back to 1996 for both KP regions.

## Outcomes

The primary outcome was a composite that included the following 4 CV events: (1) acute myocardial infarction or a coronary revascularization procedure, (2) unstable angina, (3) combined stroke (ischemic stroke or transient ischemic attack [TIA]), and (4) sudden cardiac death. Outcomes were identified from inpatient hospitalizations, using *ICD-9-CM* diagnosis codes and procedures based on Current Procedure Terminology codes. The diagnosis codes for acute myocardial infarction, unstable angina, and stroke needed to be in the primary position (principal diagnosis code) for it to be considered an outcome. For TIA, an inpatient or emergency department *ICD-9-CM* code was deemed acceptable. The criteria used to identify CV outcomes have been validated in KP and similar systems and are associated with high positive predictive values.<sup>14-20</sup> Identification of sudden cardiac death was based on a previously published algorithm<sup>21</sup> and using KP internal death information along with state death certificate data. Details of the definitions, codes, and criteria used to identify each outcome are included in the eTable in the Supplement.

## Baseline Conditions and Comorbidities

To control for baseline comorbidities in the analysis, general demographic information (age, race, median household income from US census block data), diagnosed CV risk factors (congestive heart failure, diabetes, hypertension, dyslipidemia, obesity, chronic obstructive pulmonary disease), other conditions of interest (obstructive sleep apnea, depression, erectile dysfunction), a comorbidity score (Elixhauser score),<sup>22,23</sup> and baseline laboratory testing results (testosterone levels, prostate-specific antigen [PSA], low-density lipoprotein cholesterol, and glycosylated hemoglobin) were captured. Race information from the research databases is determined using a combination of patient self-report and clinical and administrative databases. This information was collected because TRT and CV outcomes can vary by race.

## Statistical Analysis

For the primary analysis, the population of androgen-deficient patients was restricted to those with a morning testosterone level, defined as a blood test prior to 11:00 AM. Baseline characteristics for the eligible androgen-deficient men are summarized using descriptive statistics. A comparison between the ever-TRT and never-TRT groups was made by conducting *t* tests for continuous variables and  $\chi^2$  tests for categorical variables.

A multivariable Cox proportional hazards regression analysis was conducted to investigate the association between TRT

and CV outcomes. In all of the multivariable models, TRT was treated as a time-varying variable to account for time delays from the index date to initiation of TRT. A propensity score methodology (inverse probability of treatment weight [IPTW]) was used to balance baseline characteristics between the ever-TRT and never-TRT groups. The IPTW procedure generates the estimated conditional probability of receiving TRT (the exposure of interest).<sup>24-26</sup> Table 1 contains all of the measured characteristics used to create the IPTW model. Missing data (ie, laboratory test results) were included in the IPTW procedure so that men without a baseline PSA test results in the ever-TRT cohort would be weighted similar to those of men without a baseline PAS test in the never-TRT cohort. After the IPTW, event rates from each group were calculated for all of the outcomes. For the final Cox model, clinically important variables, such as age, index year, baseline testosterone values, and CV comorbidity (congestive heart failure, diabetes, hypertension, dyslipidemia, prior CV events), were included. The approach, combining outcome regression after weighting by the propensity score, is called “doubly robust” estimation.<sup>27</sup> The value of this approach is that the effect estimator is still robust to misspecification of the IPTW model or main regression model. Hazard ratios and 95% CIs for predictors of CV outcomes from the final proportional hazards regression model are reported.

Separate analyses were conducted for each cardiac outcomes (acute myocardial infarction, revascularization, unstable angina, and sudden cardiac death), stroke outcomes (stroke plus TIA), and all-cause mortality. Stratified analyses focused on men younger than 65 years and 65 years or older and on men with and without baseline CV disease comorbidity (defined as those with diagnosed congestive heart failure, hypertension, dyslipidemia, obesity, diabetes, and prior CV events). Sensitivity analyses restricted follow-up to 90 days, 180 days, and 365 days of time and also restricting the analysis to those with a baseline testosterone level less than 300 ng/dL. All analyses were conducted using SAS statistical software (version 9.2; SAS Institute Inc). A 2-sided *P* < .05 was considered statistically significant.

## Results

A total of 129 544 men were identified as having androgen deficiency either by diagnosis or having a low testosterone level. Of these individuals, 44 335 met the age and eligibility requirements for inclusion in the primary analysis; the final population consisted of 8808 men (19.8%) ever dispensed TRT and 35 527 (80.2%) never dispensed TRT. For this population 97.1% (43 049 of 44 335) entered the cohort based on a serum testosterone level of less than 300 ng/dL, and 2.9% (1286 of 44 335) were entered into the cohort based on a diagnosis of androgen deficiency. Patients who entered the cohort based on a serum testosterone level could have a subsequent diagnosis of androgen deficiency. The Figure provides breakdown of patient disposition by inclusion and exclusion criteria.

The largest proportion of men (39.6% [17 570 of 44 335]) was 40 to 55 years old, and 29.2% (12 964 of 44 335) were older

**Table 1. Baseline Characteristics (Demographic and Comorbid Disease) for the Androgen-Deficient Cohort Before and After Inverse Probability Treatment Weight (IPTW) Adjustment**

Demographics	Baseline Characteristics Without IPTW, No. (%)			Baseline Characteristics With IPTW, No. (%)		
	TRT-Never (n = 35527)	TRT-Ever (n = 8808)	P Value	TRT-Never (n = 35611)	TRT-Ever (n = 8655)	P Value
KP region			<.001			.05
Northern California	19 019 (53.5)	3008 (34.2)		17 635 (49.5)	4183 (48.3)	
Southern California	16 508 (46.5)	5800 (65.8)		17 976 (50.5)	4472 (51.7)	
Age categories, y			<.001			.29
40-55	13 824 (38.9)	3746 (42.5)		14 097 (39.6)	3405 (39.3)	
56-65	10 902 (30.7)	2899 (32.9)		11 094 (31.1)	2646 (30.6)	
>65	10 801 (30.4)	2163 (24.6)		10 420 (29.3)	2604 (30.1)	
Index 2 y			<.001			.37
1999-2000	5650 (15.9)	1045 (11.9)		5374 (15.1)	1317 (15.2)	
2001-2002	6087 (17.1)	1079 (12.3)		5745 (16.1)	1458 (16.8)	
2003-2004	4981 (14.0)	1008 (11.4)		4807 (13.5)	1207 (14.0)	
2005-2006	4732 (13.3)	1257 (14.3)		4803 (13.5)	1149 (13.3)	
2007-2008	5695 (16.0)	1823 (20.7)		6060 (17.0)	1438 (16.6)	
2009-2010	8382 (23.6)	2596 (29.5)		8822 (24.8)	2086 (24.1)	
Race/ethnicity			<.001			.54
White	19 497 (54.9)	5609 (63.7)		20 194 (56.7)	4923 (56.9)	
Black	2689 (7.6)	651 (7.4)		2681 (7.5)	686 (7.9)	
Hispanic	4740 (13.3)	1089 (12.4)		4681 (13.1)	1130 (13.1)	
Asian/Pacific Islander	3497 (9.8)	574 (6.5)		3261 (9.2)	753 (8.7)	
Unknown	5104 (14.4)	885 (10.0)		4794 (13.5)	1163 (13.4)	
Income, \$			<.001			.69
<45K	7370 (20.7)	1687 (19.2)		7283 (20.5)	1803 (20.8)	
45K-80K	17 890 (50.4)	4215 (47.9)		17 740 (49.8)	4266 (49.3)	
>80K	9799 (27.6)	2825 (32.1)		10 147 (28.5)	2486 (28.7)	
Unknown	468 (1.3)	81 (0.9)		441 (1.2)	100 (1.1)	
Comorbid conditions						
Hypertension	15 540 (43.7)	4030 (45.8)	<.001	15 741 (44.2)	3849 (44.5)	.65
CHF	701 (2.0)	127 (1.4)	<.001	711 (2.0)	116 (1.3)	<.001
Dyslipidemia	17 789 (50.1)	4782 (54.3)	<.001	18 128 (50.9)	4352 (50.3)	.31
COPD	1553 (4.4)	408 (4.6)	.29	1599 (4.5)	368 (4.3)	.34
OSA	769 (2.2)	248 (2.8)	<.001	804 (2.3)	198 (2.3)	.86
Depression	1976 (5.6)	870 (9.9)	<.001	2311 (6.5)	559 (6.5)	.90
Diabetes	8265 (23.3)	1940 (22.0)	.01	8200 (23.0)	1992 (23.0)	.99
Obesity	10 919 (30.7)	3256 (37.0)	<.001	11 389 (32.0)	2675 (30.9)	.05
ED	14 631 (41.2)	4123 (46.8)	<.001	15 053 (42.3)	3681 (42.5)	.65
Elixhauser index score			<.001			.71
0	20 676 (58.2)	4391 (49.9)		20 107 (56.5)	4866 (56.2)	
1	8431 (23.7)	2385 (27.1)		8693 (24.4)	2162 (25.0)	
2	3316 (9.3)	1043 (11.8)		3520 (9.9)	842 (9.7)	
≥3	3104 (8.7)	989 (11.2)		3291 (9.2)	785 (9.1)	
Prior CV event <sup>a</sup>	718 (2.0)	127 (1.4)	<.001	681 (1.9)	165 (1.9)	.97
Laboratory test results						
Serum testosterone level, ng/dL			<.001			.31
<200	7769 (21.9)	3734 (42.4)		9325 (26.2)	2350 (27.1)	
200-299	27 379 (77.1)	4868 (55.3)		25 813 (72.5)	6196 (71.6)	
300-400	248 (0.7)	138 (1.6)		303 (0.8)	68 (0.8)	
>400	131 (0.4)	68 (0.8)		170 (0.5)	41 (0.5)	

(continued)

**Table 1. Baseline Characteristics (Demographic and Comorbid Disease) for the Androgen-Deficient Cohort Before and After Inverse Probability Treatment Weight (IPTW) Adjustment (continued)**

Demographics	Baseline Characteristics Without IPTW, No. (%)			Baseline Characteristics With IPTW, No. (%)		
	TRT-Never (n = 35527)	TRT-Ever (n = 8808)	P Value	TRT-Never (n = 35611)	TRT-Ever (n = 8655)	P Value
HbA <sub>1c</sub> category, % of total hemoglobin			<.001			.01
<7.0	8400 (23.6)	2124 (24.1)		8412 (24.0)	2165 (25.0)	
7.0-7.9	2123 (6.0)	546 (6.2)		2147 (6.0)	518 (6.0)	
8.0-8.9	1191 (3.4)	267 (3.0)		1178 (3.3)	275 (3.2)	
≥9.0	1677 (4.7)	257 (2.9)		1602 (4.5)	336 (3.9)	
Unknown	22 136 (62.3)	5614 (63.7)		22 272 (62.5)	5360 (61.9)	
Serum LDL-C level, mg/dL			.34			.30
<70	930 (2.6)	226 (2.6)		951 (2.7)	204 (2.4)	
70-99	2110 (5.9)	549 (6.2)		2152 (6.0)	496 (5.7)	
100-129	2093 (5.9)	551 (6.3)		2143 (6.0)	516 (6.0)	
130-189	1722 (4.8)	436 (5.0)		1772 (5.0)	406 (4.7)	
≥190	165 (0.5)	52 (0.6)		167 (0.5)	45 (0.5)	
Unknown	28 507 (80.2)	6994 (79.4)		28 426 (79.8)	6988 (80.7)	
PSA category, ng/mL			<.001			.18
≤4	21 638 (60.9)	5834 (66.2)		22 091 (62.0)	5372 (62.1)	
>4	2276 (6.4)	207 (2.4)		1992 (5.6)	526 (6.1)	
Unknown	11 613 (32.7)	2767 (31.4)		11 528 (32.4)	2757 (31.8)	

Abbreviations: ED, erectile dysfunction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ED, erectile dysfunction; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; IPTW, inverse probability treatment weight; K, \$1000; KP, Kaiser Permanente; LDL-C, low-density lipoprotein cholesterol; OSA, obstructive sleep apnea; PSA, prostate-specific antigen.

SI conversion factors: To convert LDL-C to millimoles per liter, multiply by

0.0259; to convert HbA<sub>1c</sub> to proportion of total hemoglobin, multiply by 0.01; to convert testosterone to nanomoles per liter, multiply by 0.0347.

<sup>a</sup> Prior CV events include acute myocardial infarction, coronary revascularization, unstable angina, stroke, and transient ischemic attack.

than 65 years (Table 1). Rates of treatment for androgen-deficient men steadily increased over time from 15.6% from 1999 to 2000 to 23.6% from 2009 to 2010. Stratified by age categories, the treatment rate was similar for men 40 to 55 years old and 56 to 65 years old but was lower in category of those older than 65 years. Overall, 51.6% of the prescriptions were for injectable products, 34.7% for testosterone gel, and 13.6% for testosterone patches. For the treated patients, 76% (6694 of 8808) received 2 or more testosterone prescriptions, and in these patients the mean (SD) duration of TRT was 925 (819) days. A higher percentage of whites and those with a median household income greater than \$80 000 received a testosterone prescription. In general, prior to IPTW adjustment, CV risk factors were higher in the ever-TRT group at baseline. Exceptions to this were diabetes (23.3% in the never-TRT vs 22.0% in the ever-TRT groups) and CV events at baseline (2.0% in the never-TRT vs 1.4% in the ever-TRT groups). Although statistically significant, the absolute differences between groups prior to IPTW were not large. After IPTW adjustment, the balance in baseline characteristics between the ever-TRT and never-TRT groups was improved (Table 1).

In patients receiving TRT, the serum testosterone levels increased from a median of 212 ng/dL (IQR, 160-253 ng/dL) at baseline to 318 ng/dL (IQR, 237-435 ng/dL) during follow-up. Following IPTW adjustment, a higher percentage of composite CV events were seen in the never-TRT vs the ever-TRT groups, 10.2% (3650 events) vs 8.2% (711 events), respec-

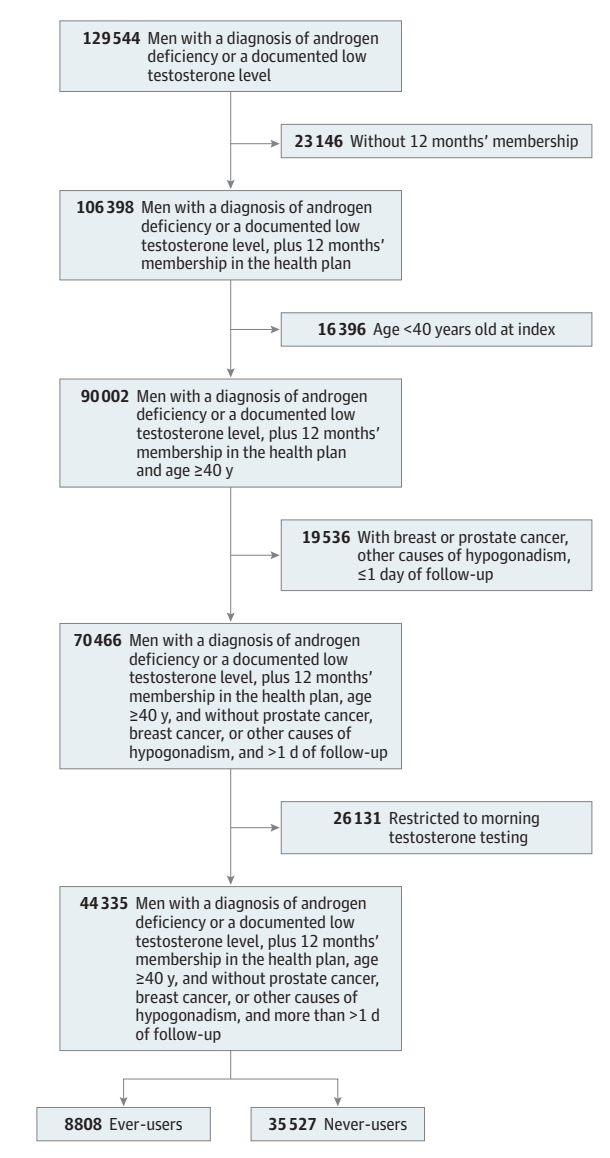
tively, during a median of 3.4 years follow-up (IQR, 1.7- 6.5 years; mean, 4.4 years). The rate of composite CV events was 23.9 per 1000 person-years in the never-TRT group vs 16.9 per 1000 person-years in the ever-TRT group.

The proportionality assumptions were met for the Cox proportional hazards model. The adjusted HR for the composite CV outcome in the ever-TRT group was 0.67 (95% CI, 0.62-0.73) (Table 2). We further explored whether a different propensity score model approach, without doubly robust estimation, produced consistent results. When applying only IPTW weighting, but not adding covariates to the multivariable Cox model, the HR was 0.66 (95% CI, 0.60-0.73), which is consistent with the main results. The HRs for the cardiac (acute myocardial infarction, revascularization procedures, sudden cardiac death, and unstable angina combined) and combined stroke (stroke and TIA) outcomes were similar to those of the primary analysis (Table 3). For the combined stroke outcome the HR was 0.72 (95% CI, 0.62-0.84) and for the cardiac outcome the HR was 0.66 (95% CI, 0.60-0.72). When broken down by the individual components of the cardiac and combined stroke outcomes the HR results were also consistent with the primary analysis results (Table 3).

The results of the stratified analyses in which populations were restricted to men younger than 65 years and those 65 years or older or those with and without baseline CV comorbidity were also consistent with the primary analysis results (Table 4), and sensitivity analysis where follow-up was



Figure. Patient Disposition (January 1, 1999, to December 31, 2010)



restricted to 90, 180, or 365 days produced similar results. Patients receiving topical TRT had slightly higher rates of composite CV events compared with those receiving injectable TRT, 15.5 per 1000 person-years vs 14.5 per 1000 person-years, respectively, with an adjusted HR of 1.02 (95% CI, 1.00-1.05).

## Discussion

In this study of androgen-deficient men, TRT was associated with a decreased risk of CV events. These results were consistent in analyses stratified by age, the presence or absence of baseline CV risk factors, and in a sensitivity analysis in which follow-up was restricted to the first 90, 180, or 365 days. While these findings differ from those of recently published observational studies of TRT, they are consistent with other evidence of CV risk and the benefits of TRT in androgen-deficient men.

Table 2. Complete Proportional Hazard Model Results for Composite CV Events in the Androgen-Deficient Cohort

Model Covariates	Time Varying TRT With IPTW	
	HR (LB-UB 95% CI)	P Value
Testosterone treatment	0.67 (0.62-0.73)	<.001
Region, SC vs NC	1.07 (1.01-1.13)	.03
Age category, y		
40-55	1 [Reference]	
56-65	1.81 (1.66-1.98)	<.001
>65	2.82 (2.59-3.06)	<.001
Index year		
2009-2010	1 [Reference]	
2007-2008	1.22 (1.06-1.40)	.005
2005-2006	1.42 (1.23-1.63)	<.001
2003-2004	1.67 (1.46-1.92)	<.001
2001-2002	1.99 (1.75-2.27)	<.001
1999-2000	2.41 (2.11-2.75)	<.001
Elixhauser index score		
0	1 [Reference]	
1	1.37 (1.27-1.47)	<.001
2	1.61 (1.45-1.78)	<.001
≥3	2.21 (1.99-2.46)	<.001
Congestive heart failure	1.60 (1.38-1.87)	<.001
Diabetes	1.40 (1.31-1.50)	<.001
Hypertension	1.20 (1.12-1.28)	<.001
Dyslipidemia	1.47 (1.37-1.58)	<.001
Testosterone, ng/dL		
<200	1 [Reference]	
200-299	0.85 (0.80-0.91)	<.001
300-400	0.76 (0.52-1.10)	.14
>400	1.64 (1.06-2.54)	.03
Prior cardiovascular events <sup>a</sup>	1.97 (1.75-2.26)	<.001

Abbreviations: CV, cardiovascular; IPTW, inverse probability of treatment weight; LB, lower bound; NC, Northern California Kaiser; SC, Southern California Kaiser; TRT, testosterone replacement therapy; UB, upper bound.

SI conversion factor: To convert testosterone to nanomoles per liter, multiply by 0.0347.

<sup>a</sup> Prior CV events include acute myocardial infarction, coronary revascularization, unstable angina, stroke, and transient ischemic attack.

Low serum testosterone levels in aging men have been associated with an increased risk of coronary artery disease.<sup>28-30</sup> Other studies have reported an inverse relationship between serum testosterone and carotid intima thickness.<sup>31-33</sup> Testosterone replacement therapy in androgen-deficient men has also been shown to have beneficial effects on metabolic profiles with increased insulin sensitivity, lower blood glucose levels, and lower hemoglobin A<sub>1c</sub> values.<sup>34,35</sup> In addition, TRT has been associated with reductions in total body weight, increases in lean body mass, and decreased body mass index.<sup>34,36,37</sup> These data lend support to the findings that TRT is associated with lower rates of adverse CV outcomes in androgen-deficient men.

Other studies have reported beneficial associations for TRT in men with low testosterone levels.<sup>8,9</sup> Shores et al<sup>8</sup> found that in men with a baseline serum testosterone level of

**Table 3. Proportional Hazard Model (Testosterone Treatment Time Varying With IPTW): CV Outcomes Broken Down by Individual Components With HRs, Event Counts, and Rates in the Androgen-Deficient Cohort**

Individual CV Component	Summary Counts by Treatment Group				Time Varying TRT With IPTW <sup>a</sup>	
	TRT-Never		TRT-Ever		HR (LB-UB 95% CI)	P Value
	CV Event, No.	Event Rate, per 1000 Person-years <sup>b</sup>	CV Event, No.	Event Rate, per 1000 Person-years		
Combined stroke	929	5.8	196	4.3	0.72 (0.62-0.84)	<.001
Stroke	501	3.1	95	2.1	0.64 (0.52-0.80)	<.001
TIA	428	2.7	101	2.2	0.82 (0.66-1.02)	.07
Cardiac event	2780	18.2	524	11.9	0.66 (0.60-0.72)	<.001
AMI	962	6.3	204	4.7	0.74 (0.63-0.86)	<.001
Revascularization	867	5.7	147	3.4	0.59 (0.49-0.70)	<.001
SCD	496	3.3	106	2.4	0.76 (0.61-0.93)	.009
Unstable angina	455	3.0	67	1.5	0.52 (0.41-0.68)	<.001
Death						
All-cause death	4088	23.1	864	16.7	0.72 (0.67-0.77)	<.001

Abbreviations: AMI, acute myocardial infarction; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weight; LB, lower bound; revascularization, coronary artery bypass graft and percutaneous transluminal coronary angioplasty; SCD, sudden cardiac death; TIA, transient ischemic attack; TRT, testosterone replacement therapy; UB, upper bound.

<sup>a</sup> IPTW based on all patient characteristics included in Table 1 with doubly robust

estimation, controlling for age, Kaiser Permanente region, index year, Elixhauser comorbidity score, congestive heart failure, dyslipidemia, diabetes, hypertension, prior cardiovascular events, and baseline testosterone.

<sup>b</sup> Event rates per 1000 person-years were calculated after applying IPTW.

**Table 4. Proportional Hazard Model: Stratified, and Sensitivity Analyses With HRs, Event Counts, and Rates in the Androgen-Deficient Cohort**

Model	Summary Counts by Treatment Group				Time Varying TRT With IPTW <sup>a</sup>	
	TRT-Never		TRT-Ever		HR (LB-UB 95% CI)	P Value
	CV Event, No.	Event Rate per 1000 Person-years <sup>b</sup>	CV Event, No.	Event Rate per 1000 Person-years <sup>b</sup>		
Stratified analyses using composite CV events outcome						
Age, y						
≥65	1985	42.2	327	27.7	0.68 (0.60-0.76)	<.001
<65	1705	16.2	351	10.9	0.66 (0.59-0.72)	<.001
CV comorbidity	2720	29.9	529	19.5	0.65 (0.59-0.71)	<.001
No CV comorbidity	924	15.0	187	11.4	0.76 (0.65-0.89)	<.001
Sensitivity analysis, restricting follow-up time						
90 d	228	23.2	19	15.6	0.45 (0.25-0.80)	.007
180 d	456	24.2	40	14.6	0.60 (0.43-0.84)	.003
365 d	806	22.4	82	13.9	0.59 (0.46-0.75)	<.001
Sensitivity analysis, restricting to baseline testosterone levels <300 ng/dL	3610	24.0	703	16.2	0.67 (0.62-0.73)	<.001

Abbreviations: Composite CV events, acute myocardial infarction, coronary revascularization, unstable angina, stroke, transient ischemic attack, and sudden cardiac death; CV comorbidities, congestive heart failure, hypertension, dyslipidemia, obesity, diabetes, or prior cardiovascular events; Dx, diagnoses; HR, hazard ratio; IPTW, inverse probability of treatment weight (note: IPTW was recalculated for each analysis in this table); LB, lower bound; stroke, stroke and transient ischemic attack; TRT, testosterone replacement therapy; UB, upper bound.

SI conversion factor: To convert testosterone to nanomoles per liter, multiply by 0.0347.

<sup>a</sup> Doubly robust estimation, controlled for age, Kaiser Permanente region, index year, Elixhauser comorbidity score, congestive heart failure, dyslipidemia, diabetes, hypertension, prior CV events, and baseline testosterone.

<sup>b</sup> Event rates per 1000 person-years were calculated after applying IPTW.

250 ng/dL or less, TRT was associated with a 39% reduction in all-cause mortality (adjusted HR, 0.61; 95% CI, 0.42-0.88). Sharma et al<sup>9</sup> studied the relationship between normalization of testosterone levels following TRT and all-cause mortality and CV events in men with low testosterone levels at baseline. Patients were divided into 3 groups based on receipt of TRT and whether serum testosterone level normalized in the

TRT cohorts (ie, no treatment, TRT with normalization of serum testosterone, and TRT without normalization of serum testosterone).<sup>9</sup> Compared with no treatment or TRT without normalization of serum testosterone, patients receiving TRT with normalization of serum testosterone had a lower risk of all-cause mortality, myocardial infarction, and stroke (adjusted HR, 0.44; 95% CI, 0.42-0.46 for mortality in patients

receiving TRT who normalized their serum testosterone compared with no treatment).<sup>9</sup>

The results of this study are counter to 2 other observational studies that found a higher risk of adverse CV outcomes in patients receiving TRT.<sup>6,7</sup> Vigen et al<sup>6</sup> selected a population of men with low testosterone levels who had undergone coronary angiography and found that the risk of adverse CV outcomes was elevated (HR, 1.29; 95% CI, 1.04-1.58). Questions have been raised about the analysis and study findings given the fact that the unadjusted rates of adverse CV outcomes were twice as high in the untreated cohort (21.2%) vs the treated cohort (10.1%).<sup>10</sup> The patients studied by Vigen et al<sup>6</sup> also had a high CV disease burden based on study eligibility criteria; at baseline 92.5% had hypertension, 88.0% had hyperlipidemia, 55.4% had diabetes, 54.4% were obese, and 23.7% had a prior myocardial infarction. Using a large health care claims database, Finkle et al<sup>7</sup> conducted a self-controlled case series analysis (in which individuals served as their own controls) to study nonfatal acute myocardial infarction in the 90 days following a testosterone prescription relative to the rate prior to the prescription. The postprescription vs preprescription rate ratio for nonfatal acute myocardial infarction was 1.36 (95% CI, 1.03-1.81).<sup>7</sup> Serum testosterone levels were not available, and the analysis was not restricted to those with a diagnosis of androgen deficiency; therefore, these results may not be generalizable to patients with an indication for TRT. Moreover, if having a nonfatal MI influences the likelihood of receiving a testosterone prescription, the results from this type of analysis may be biased.

It has been reported that 25% to 40% of men receiving testosterone prescriptions do not have baseline testosterone levels measured.<sup>38,39</sup> The lack of baseline testosterone testing in patients receiving TRT is a concern. In the primary analysis, men with a baseline serum testosterone level greater than 400 ng/dL had a higher adjusted HR for the composite CV outcome (HR, 1.64; 95% CI, 1.06-2.54) compared with those with lower baseline testosterone. While the data from this study are preliminary and only a small percentage of patients had a baseline testosterone level greater than 400 ng/dL (0.4% in the never-TRT vs 0.8% in the ever-TRT cohorts), these findings suggest caution when using TRT in men with normal testosterone levels.

### Limitations

There are several potential limitations that need to be considered when evaluating the results of this study. First, the criterion for identifying androgen-deficient males ( $\geq 1$  morning testosterone level or a diagnosis) does not meet the strict criteria set forth by the Endocrine Society.<sup>3</sup> Therefore some individuals in this study could be misclassified as being androgen-deficient. Obtaining 2 or more testosterone levels prior to

initiating TRT does not seem to be common in clinical practice. Layton et al<sup>39</sup> reported that 40% of patients treated with testosterone had no baseline testosterone levels, 50% had a single test, and only 10% had multiple tests prior to treatment initiation. In the current study, 6% of patients had multiple testosterone tests done before initiating treatment. Second, owing to the observational design of the study, unmeasured confounding may have had an influence on the results; unmeasured confounders could possibly influence clinicians to selectively use testosterone in healthier patients. Among measured confounders, however, the patients who received testosterone had a higher disease burden (Elixhauser Index) and higher percentages of common CV comorbidities. Moreover, the time frame for this study was prior to reports about CV risk, limiting the risk of confounding by indication. Third, not all of the possible CV risk factors, such as diet, exercise, and family history, are easily retrievable from the EMR and were therefore not included in the analysis. This, however, is true for both the ever-TRT and never-TRT cohorts, and any bias would likely be nondifferential. Fourth, a competing risks analysis was not conducted. Although the androgen-deficient cohort had high rates of CV comorbidities, they were relatively young, and other causes of death were not considered substantial. In addition, separate analyses were conducted for cardiac and stroke outcomes that necessitated generation of distinct subcohorts to accommodate the change in censoring events and the findings remained consistent. Fifth, ascertainment bias could exist if patients dispensed TRT were followed more closely than those without TRT. While this is a possibility, men in both the ever-TRT and never-TRT groups had higher rates of CV comorbidities than the general population and therefore were seen frequently in the clinic by their primary care and physician specialists. Sixth, dose and duration of testosterone use were not designed into the analysis, primarily because studies finding an increased CV risk postulated that this was an acute effect of testosterone.<sup>7</sup> Given the underlying mechanisms associated with CV risk, additional studies should be conducted to determine the impact of testosterone dose and duration. Seventh, some untreated patients may have been misclassified owing to use of outside pharmacies to obtain their TRT. To minimize this, the analysis was restricted to those patients with a drug-benefit that provides member incentives to obtain their prescriptions at a KP pharmacy.

### Conclusions

Among men with androgen deficiency, dispensed testosterone prescriptions were associated with a lower risk of CV outcomes over a median 3.4 years of follow-up.

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## REFERENCES

- Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab*. 2001;86(2):724-731.
- Zmuda JM, Cauley JA, Kriska A, Glynn NW, Gutai JP, Kuller LH. Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men: a 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. *Am J Epidemiol*. 1997;146(8):609-617.
- Bhasin S, Cunningham GR, Hayes FJ, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95(6):2536-2559.
- Snyder PJ, Bhasin S, Cunningham GR, et al; Testosterone Trials Investigators. Effects of testosterone treatment in older men. *N Engl J Med*. 2016;374(7):611-624.
- Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363(2):109-122.
- Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013;310(17):1829-1836.
- Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014;9(1):e85805.
- Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab*. 2012;97(6):2050-2058.
- Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J*. 2015;36(40):2706-2715.
- Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM. Testosterone therapy and cardiovascular risk: advances and controversies. *Mayo Clin Proc*. 2015;90(2):224-251.
- Corona G, Rastrelli G, Monami M, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol*. 2011;165(5):687-701.
- Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2014;13(10):1327-1351.
- Koebnick C, Langer-Gould AM, Gould MK, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. *Perm J*. 2012;16(3):37-41.
- Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellsague J, Griffin MR. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. *Pharmacoepidemiol Drug Saf*. 2008;17(1):20-26.
- Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):100-128.
- Cutrona SL, Toh S, Iyer A, et al. Validation of acute myocardial infarction in the Food and Drug Administration's Mini-Sentinel program. *Pharmacoepidemiol Drug Saf*. 2013;22(1):40-54.
- Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362(23):2155-2165.
- Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. *Pharmacoepidemiol Drug Saf*. 2010;19(6):596-603.
- Choma NN, Griffin MR, Huang RL, et al. An algorithm to identify incident myocardial infarction using Medicaid data. *Pharmacoepidemiol Drug Saf*. 2009;18(11):1064-1071.
- Varas-Lorenzo C, Castellsague J, Stang MR, Tomas L, Aguado J, Perez-Gutthann S. Positive predictive value of ICD-9 codes 410 and 411 in the identification of cases of acute coronary syndromes in the Saskatchewan Hospital automated database. *Pharmacoepidemiol Drug Saf*. 2008;17(8):842-852.
- Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. *Pharmacoepidemiol Drug Saf*. 2010;19(6):563-572.
- Austin SR, Wong YN, Uzzo RG, Beck JR, Eggleston BL. Why summary comorbidity measures such as the Charlson Comorbidity Index and Elixhauser Score work. *Med Care*. 2015;53(9):e65-e72.
- Sharabiani MTA, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. *Med Care*. 2012;50(12):1109-1118.
- Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol*. 2006;163(3):262-270.
- Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Stat Med*. 2010;29(20):2137-2148.
- Brookhart MA, Wyss R, Layton JB, Stürmer T. Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes*. 2013;6(5):604-611.
- Funk MJ, Westreich D, Wiesen C, Stürmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. *Am J Epidemiol*. 2011;173(7):761-767.
- Rosano GMC, Sheiban I, Massaro R, et al. Low testosterone levels are associated with coronary artery disease in male patients with angina. *Int J Impot Res*. 2007;19(2):176-182.
- Akishita M, Hashimoto M, Ohike Y, et al. Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. *Atherosclerosis*. 2010;210(1):232-236.
- Hu X, Rui L, Zhu T, et al. Low testosterone level in middle-aged male patients with coronary artery disease. *Eur J Intern Med*. 2011;22(6):e133-e136.
- De Pergola G, Pannaciuilli N, Ciccone M, Tartagni M, Rizzon P, Giorgino R. Free testosterone plasma levels are negatively associated with the intima-media thickness of the common carotid artery in overweight and obese glucose-tolerant young adult men. *Int J Obes Relat Metab Disord*. 2003;27(7):803-807.
- Mäkinen J, Järvisalo MJ, Pöllänen P, et al. Increased carotid atherosclerosis in andropausal middle-aged men. *J Am Coll Cardiol*. 2005;45(10):1603-1608.
- Soisson V, Brailly-Tabard S, Empana JP, et al. Low plasma testosterone and elevated carotid intima-media thickness: importance of low-grade inflammation in elderly men. *Atherosclerosis*. 2012;223(1):244-249.
- Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl*. 2009;30(6):726-733.
- Jones TH, Arver S, Behre HM, et al; TIMES2 Investigators. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care*. 2011;34(4):828-837.
- Svartberg J, Agledahl I, Figneschau Y, Sildnes T, Waterloo K, Jorde R. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *Int J Impot Res*. 2008;20(4):378-387.
- Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2010;95(2):639-650.
- Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS. Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern Med*. 2013;173(15):1465-1466.
- Layton JB, Li D, Meier CR, et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. *J Clin Endocrinol Metab*. 2014;99(3):835-842.