

Original Investigation

Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels

A Randomized Clinical Trial

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IMPORTANCE Testosterone use in older men is increasing, but its long-term effects on progression of atherosclerosis are unknown.

OBJECTIVE To determine the effect of testosterone administration on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels.

DESIGN, SETTING, AND PARTICIPANTS Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) was a placebo-controlled, double-blind, parallel-group randomized trial involving 308 men 60 years or older with low or low-normal testosterone levels (100-400 ng/dL; free testosterone <50 pg/mL), recruited at 3 US centers. Recruitment took place between September 2004 and February 2009; the last participant completed the study in May 2012.

INTERVENTIONS One hundred fifty-six participants were randomized to receive 7.5 g of 1% testosterone and 152 were randomized to receive placebo gel packets daily for 3 years. The dose was adjusted to achieve testosterone levels between 500 and 900 ng/dL.

MAIN OUTCOMES AND MEASURES Coprimary outcomes included common carotid artery intima-media thickness and coronary artery calcium; secondary outcomes included sexual function and health-related quality of life.

RESULTS Baseline characteristics were similar between groups: patients were a mean age of 67.6 years; 42% had hypertension; 15%, diabetes; 15%, cardiovascular disease; and 27%, obesity. The rate of change in intima-media thickness was 0.010 mm/year in the placebo group and 0.012 mm/year in the testosterone group (mean difference adjusted for age and trial site, 0.0002 mm/year; 95% CI, -0.003 to 0.003, $P = .89$). The rate of change in the coronary artery calcium score was 41.4 Agatston units/year in the placebo group and 31.4 Agatston units/year in the testosterone group (adjusted mean difference, -10.8 Agatston units/year; 95% CI, -45.7 to 24.2; $P = .54$). Changes in intima-media thickness or calcium scores were not associated with change in testosterone levels among individuals assigned to receive testosterone. Sexual desire, erectile function, overall sexual function scores, partner intimacy, and health-related quality of life did not differ significantly between groups. Hematocrit and prostate-specific antigen levels increased more in testosterone group.

CONCLUSIONS AND RELEVANCE Among older men with low or low-normal testosterone levels, testosterone administration for 3 years vs placebo did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium nor did it improve overall sexual function or health-related quality of life. Because this trial was only powered to evaluate atherosclerosis progression, these findings should not be interpreted as establishing cardiovascular safety of testosterone use in older men.

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Testosterone sales have increased substantially, particularly among older men, during the past decade.¹ However, the benefits and risks of long-term testosterone administration to older men with age-related decline in testosterone levels remain poorly understood.²

A randomized trial of testosterone involving older men with mobility limitations,³ stopped early due to the increased frequency of cardiovascular adverse events in the testosterone group, and some,^{4,5} but not other,⁶ retrospective analyses of testosterone users have raised concern that testosterone administration might increase the risk of cardiovascular disease (CVD) events. Although some studies have reported an association of low testosterone levels with increased risk of diabetes, metabolic syndrome, proatherogenic dyslipidemia, CVD, and mortality,^{2,7-11} other studies have not shown a consistent association between testosterone levels and incident CVD.² Testosterone levels have been negatively associated with common carotid artery intima-media thickness in some studies.^{2,11} The data from preclinical models have also been conflicting. In low-density lipoprotein receptor-deficient mice, orchiectomy accelerates and testosterone supplementation retards aortic atherogenic lesions.¹² However, the long-term consequences of testosterone supplementation on atherosclerosis in older men remain unknown.

The primary aim of the Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) trial was to determine the effect of increasing circulating testosterone concentrations into a range that is mid-normal for young men on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels. The secondary aim was to determine the effects on sexual function and health-related quality of life (QOL).

Methods

Study Design

The TEAAM trial was a randomized, placebo-controlled, parallel-group, double-blind trial. The study protocol was approved by institutional review boards at the 3 participating institutions: Charles Drew University, Los Angeles, California; Boston University Medical Center, Brigham and Women's Hospital, Boston, Massachusetts; and by the Western Institutional Review Board, Puyallup, Washington, for the Kronos Longevity Research Institute, Phoenix, Arizona (see the study protocol in [Supplement 1](#) and the revised statistical analysis plan in [Supplement 2](#)). Study recruitment took place September 2004 through February 2009; the last participant completed the study in May 2012. All participants provided written, informed consent. The data and safety monitoring board reviewed adverse events semiannually.

Participants

The participants were community-dwelling men, 60 years or older, with total morning (7-10 AM) testosterone levels between 100 and 400 ng/dL or free testosterone less than 50 pg/mL. We excluded men who had diseases of the testes, pituitary, or hypothalamus; prostate cancer; breast cancer; or

cancers other than nonmelanotic skin cancers; severe lower urinary tract symptoms (International Prostate Symptom Score [IPSS] >21); prostate-specific antigen (PSA) levels higher than 4 ng/mL; dementia; untreated major depression or schizophrenia; alanine aminotransferase and aspartate aminotransferase more than 3 times the upper limit of normal; creatinine levels higher than 2.5 mg/dL; hemoglobin A_{1c} greater than 9.0%; hematocrit greater than 48%; unstable angina; New York Heart Association class III or IV heart failure; myocardial infarction within 6 months of entry; untreated thyroid disease; systolic blood pressure (BP) higher than 160 mm Hg or diastolic BP higher than 100 mm Hg; or body mass index (BMI) higher than 35, calculated as weight in kilograms divided by height in meters squared. (To convert creatinine from mg/dL to μ mol/L, multiply by 88.4.)

Race/ethnicity was based on self-report. Although the study was not powered to test specific hypotheses related to race or ethnicity, black men have a higher risk of clinical prostate cancer. There has been concern that they may be at increased risk of developing clinical prostate cancer during testosterone therapy.

Randomization

Participants were assigned using a 1:1 concealed randomization and stratification by age (60-75 years and >75 years) and site to receive either placebo or testosterone gel. A statistician generated the randomization sequence and forwarded it to the investigational drug pharmacy, which then assigned participants a randomization number.

Intervention

Eligible participants were randomized to receive either 7.5 g of 1% testosterone gel (75 mg of testosterone) or placebo gel daily for 3 years. Two weeks after randomization, total testosterone levels were measured 2 to 12 hours after gel application. If the total testosterone concentration was lower than 500 ng/dL, the testosterone dose was increased to 10 g or if higher than 900 ng/dL, reduced to 5 g daily. At the same time, the placebo dose was adjusted for another participant in the placebo group by an unblinded observer to maintain blinding.

Blinding

The study staff and participants were blinded. All participants received 3 gel packets daily to maintain blinding (eg, men randomized to receive 7.5 g of testosterone gel received 1 packet containing 5.0 g of testosterone gel, 1 containing 2.5 g of testosterone gel, and 1 containing placebo gel, whereas those in the placebo group received 3 placebo packets). The effectiveness of blinding was not assessed.

Outcomes

The coprimary outcomes were the rate of change in distal right common carotid artery intima-media thickness and coronary artery calcium. Common carotid artery intima-media thickness, which is predictive of incident cardiovascular events,^{13,14} was measured at baseline and every 6 months during the intervention period. We also assessed the total calcium score

using multidetector-row computed tomography (MDCT), another measure of subclinical atherosclerosis,¹⁵ at baseline and at 18 and 36 months. Serum lipids and fasting glucose concentrations were measured at 0, 6, 18, and 36 months. Safety assessments included adverse event recording, hematocrit, blood chemistries, PSA, and IPSS values. We also report herein the results of some secondary efficacy outcomes—sexual function and health-related QOL.

Outcome Assessments

B-mode carotid artery images for intima-media thickness were acquired from the far wall of the distal centimeter of the right carotid artery with high-resolution ultrasound equipment, calibrated using a phantom and cardiac gating using standardized methods for reproducing transducer angulation.^{14,16} Ultrasonographers were certified by the University of Southern California Core Imaging Center. Ultrasound images were analyzed using automated boundary detection to locate lumen-intima and media-adventitia boundaries at subpixel resolution (eAppendix B in [Supplement 3](#)). The coefficient of variation of intima-media thickness measurement was less than 4%.

The MDCT scan was performed using the General Electric Lightspeed Model VCT 64 channel scanner in high-resolution volume mode, using 100-millisecond exposure time.¹⁵ Electrocardiographic-triggering synchronized images in the same point in diastole, corresponding to 40% of the R-R interval (eAppendix B in [Supplement 3](#)). Proximal coronary arteries were visualized, and at least 30 consecutive images were obtained at 3-mm intervals. *Coronary calcium* was defined as a plaque of at least 3 contiguous pixels (area, 1.02 mm²) with a density of more than 130 Hounsfield units. The lesion score was calculated by multiplying lesion area by a density factor derived from Hounsfield units. The total calcium score was determined by summing the lesion scores from the left main, left anterior descending, circumflex, and right coronary arteries using the Agatston method.¹⁵ A cardiac physician trained in computed tomographic (CT) imaging who was blinded to interventions interpreted all scans at the CT reading center of the Los Angeles Biomedical Research Institute, Torrance, California (supervised by M.B.).

Sexual function was assessed using the International Index of Erectile Function (IIEF), a validated, 15-item questionnaire that assesses 5 domains of sexual function—erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall sexual satisfaction.¹⁷ The IIEF, with a possible range of 0 to 75 (higher scores representing better function), has excellent internal consistency (Cronbach α , .90) and test-retest reliability (0.82). The minimal clinically important difference for the erectile function domain of IIEF is 4 points using as the anchor response to question 7: “Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?” In a subset of participants enrolled at Boston University Medical Center, the marital interaction scale from the Cancer Rehabilitation Evaluation System Short Form was used to assess a participant’s relationship and intimacy with his sexual partner.¹⁸ The Cancer Rehabilitation Evaluation System Short Form has been validated in many settings and is

scored from 0 to 4 with lower scores representing better interaction intimacy.¹⁸

We determined whether testosterone improves self-reported physical function via the physical function domain of the Medical Outcomes Study 36-item short form health survey (SF-36)¹⁹ for all participants. Additionally, health-related QOL was assessed using the full SF-36 questionnaire¹⁹ for participants enrolled at the Boston and Los Angeles sites. The SF-36 measures 8 domains of the QOL—physical function, bodily pain, vitality, role limitations due to physical problems, general health perceptions, emotional well-being, social function, and role limitations due to emotional problems. Each domain is scored separately from 0 to 100 with higher scores representing better health-related QOL.¹⁹ The SF-36 has excellent internal consistency (Cronbach α .76-.90) and test-retest reliability (0.76-0.96) for various domains. The minimal clinically important differences for various domains of SF-36 have been determined to be between 3 and 5 for various conditions.

Hormone Assays

Total testosterone was measured at Quest Diagnostics, San Juan Capistrano, California, using a Bayer Advia Centaur immunoassay (Siemens Healthcare Diagnostics) after extraction of serum with ethyl acetate and hexane followed by celite chromatography; this assay, validated against liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), has a sensitivity of 10 ng/dL.²⁰ Sex hormone-binding globulin was measured using an immunofluorometric assay with a sensitivity of 0.24 μ g/mL (Delphia-Wallac).²¹ Free testosterone was calculated.²²

Statistical Analyses

Summary statistics, exploratory analyses, and graphical displays were used to assess observed differences at baseline and during the intervention period. The primary intent-to-treat analysis included all 306 randomized participants who received at least 1 dose of study medication. We estimated the rate of atherosclerosis progression, assessed as the rate of linear change in the carotid artery intima-media thickness and in coronary artery calcium. Primary analyses compared the rate of change in intima-media thickness and calcium between groups, controlling for stratification by age group and study center, using a mixed-effects regression model in which participants were nested within study center, which was treated as a random effect. Age-group, time-in-treatment, and treatment-by-time interaction were included as fixed effects, with the latter quantifying the estimated treatment effect. The missing data were accommodated using multiple imputation²³ in which missing outcomes values were estimated using predictive mean matching. The imputation model controlled for age group, study center, randomization, and study visit. A total of 50 imputed values were generated for each missing record, and the model was allowed to converge over 50 iterations. Analyses of each imputed data set were combined to generate pooled estimates of effects and Wald tests of statistical significance (see the revised statistical analysis plan in [Supplement 2](#)).

Secondary outcomes were analyzed similarly. The IIEF and health-related QOL data were imputed at the domain level, and composite scores constrained to match the scoring algorithm at each iteration; nonmissing domain scores were also included in the predictive model.

Sensitivity analyses were performed restricting attention to observed data (without imputation) in participants who completed the planned intervention and to subgroups of men who were obese, or had diabetes or coronary artery disease (CAD). We also considered calcium progression among individuals with no coronary calcium at baseline. Observed associations between changes in circulating testosterone levels and the primary outcomes were obtained using a generalized additive model, the utility of which was assessed using an analysis of deviance. Adverse events were organized by system organ class, and comparisons in the number of events per participant were made across trial groups using Poisson regression.

All statistical comparisons were 2-sided, and type I error probability was set at .05. The analyses were performed using R statistical software, version 3.1.2 (R Foundation for Statistical Computing) and SAS software version 9.3 (SAS Institute Inc).

Sample Size Estimation

Because no data on testosterone's effects on carotid artery intima-media thickness were available, we computed the sample size required to detect a treatment effect (between-group difference in thickness progression rate 0.008 mm/y) similar to that found in the Estrogen in the Prevention of Atherosclerosis Trial (EPAT).¹⁴ We assumed an SD of 0.02 mm/y, the SD of change found in the EPAT and in the lipid-lowering trials, Cholesterol Lowering Atherosclerosis Study (CLAS)²³ and Monitored Atherosclerosis Regression Study (MARS).²⁴ Assuming a 2-sided *P* value, α of .05, and $1 - \beta$ of .80, we estimated a cumulative exposure of 3456 participant-months (eg, 96 participants for 36 months) in each of the 2 groups would be needed to detect a treatment effect similar to what EPAT found. Conservatively, recruitment of 125 men was planned in each group, for a total of 250 men, assuming a 25% dropout rate. The treatment effect detectable with this sample size is smaller than that observed in CLAS, which yielded a hazard ratio for all coronary events of 3.1 per 0.03 mm/y.^{23,24} Therefore, enrollment of 250 men would provide more than 80% power to detect a clinically meaningful effect such as that exerted by statin therapy.^{23,24}

In a previous study,²⁵ the yearly mean (SD) rate of change in coronary artery calcium scores was 33% (12%) in asymptomatic persons. Conservatively, we assumed that the common SD is 35 Agatston units. If the rate of change in calcium were similar in placebo-treated men to that reported in the previous study,²⁵ a sample size of 250 men would provide more than 90% power to detect a 25% between-group difference in the rate of change of in either direction (eg, difference between 33% increase in calcium scores for one group vs 24% in the other). These assumptions were based on previous studies of statin effects on coronary artery calcium.²⁵

In November 2007, the data and safety monitoring board required an increase in sample size to approximately 300 men because of higher-than-expected dropout rates ($\approx 30\%$). En-

rollment of 300 participants would provide approximately 6912 months of medication exposure, which was deemed sufficient to detect the hypothesized between-group difference in intima-media thickness with 80% power.

Results

Flow of Participants Through the Study

Of 1893 eligible participants who underwent telephone screening, 1406 were invited to be screened in person. Of those, 1098 did not meet eligibility criteria or declined to participate, and 308 were randomized (Figure 1). Two withdrew consent before receiving study medication leaving 306, 155 in testosterone and 151 in placebo group. The 306 receiving at least 1 medication dose were included in primary analyses. There were 7400 cumulative person-months of drug exposure.

Participant Characteristics

The 2 groups were similar in baseline characteristics (Table), including common carotid artery intima-media thickness, coronary artery calcium, IIEF, and health-related QOL scores (Table). The mean (SD) age was 67.6 (5.2) years and body mass index, 28.1 (2.9). Of 306 participants, 128 (42%) had hypertension, 46 (15%) had diabetes, 46 (15%) had CAD, 82 (27%) were obese, and 133 (43%) were receiving a statin at randomization.

Participants completing the trial were similar in their baseline testosterone levels, intima-media thickness, calcium scores, and body mass index to those who did not complete the trial (eTable 1 in Supplement 4). Adherence to study medication, assessed by counting the number of used and unused gel packs, was 95% in both groups.

Primary and Secondary Outcomes

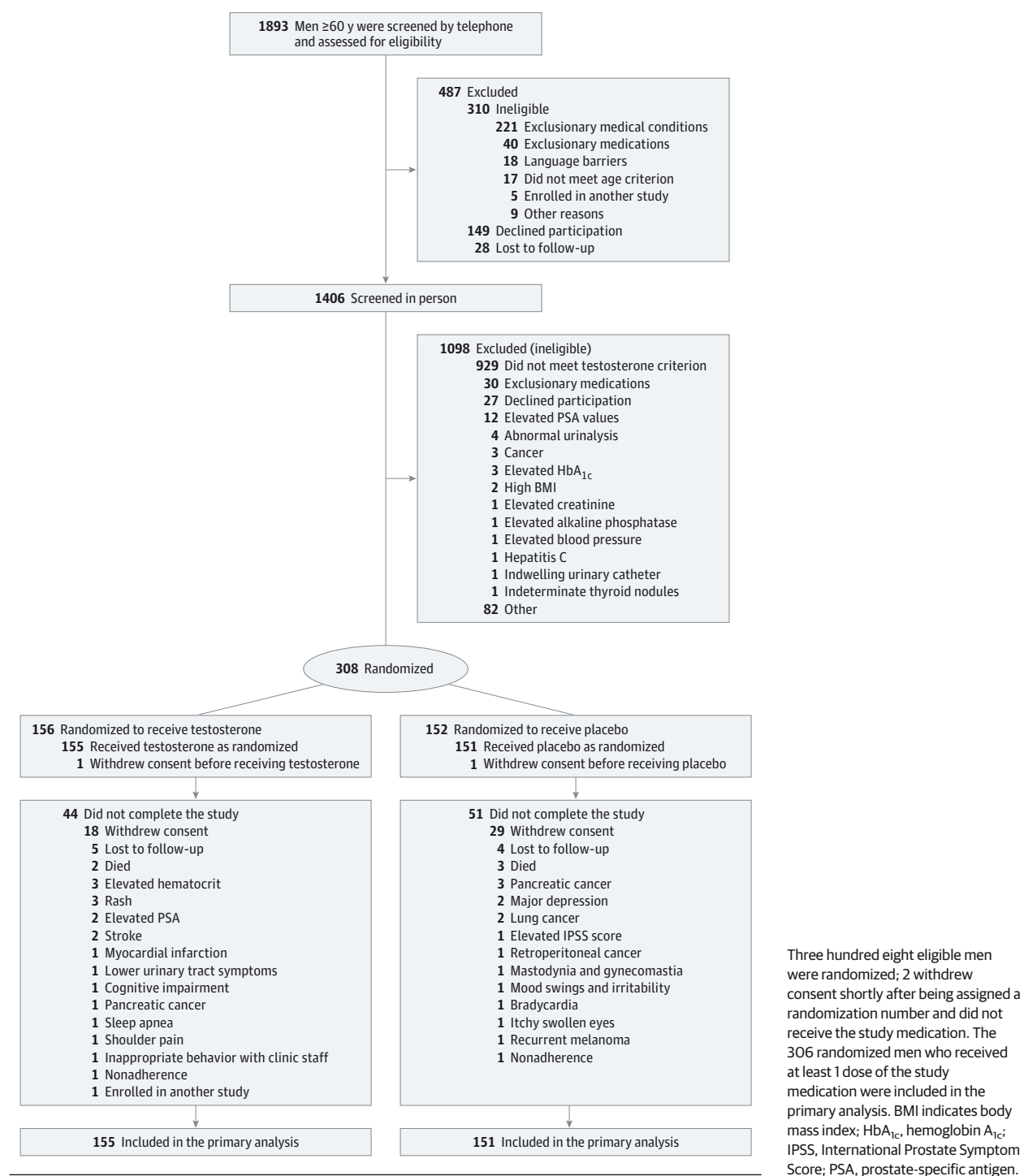
Testosterone Levels

Total and free testosterone levels were similar between groups at baseline (Table). The mean (SD)—derived from the mean of the 6-, 18-, and 36-month measurements—of total testosterone increased to 565 (245) ng/dL and the free testosterone increased to 104 (59) pg/mL in the testosterone group, whereas the placebo group's mean testosterone levels did not change significantly: 330 (103) ng/dL for total testosterone and 51 (20) ng/dL for free testosterone (Figure 2). Among the 155 men randomized to receive testosterone, the daily dose was adjusted down to 5 g for 25 men and up to 10 g in for 72 men. Among men randomized to the testosterone group, serum testosterone levels declined over time (Figure 2).

Intima-Media Thickness Scores

Exploratory assessments supported modeling of common carotid artery intima-media thickness and coronary artery calcium change as linear trends with time. Baseline mean (SD) intima-media thickness did not differ between groups (placebo, 0.879 [0.199] mm; testosterone, 0.877 [0.210] mm). Using a mixed-effects regression model, which was adjusted for age and trial site (via a random effect) and included all 306 participants, the per-year rate of change in intima-media

Figure 1. Flow of Participants Through the Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) Trial



thickness did not differ significantly between groups (mean difference, 0.0002 mm; 95% CI, -0.003 to 0.003; $P = .89$; Figure 3). The rates of change in intima-media thickness was 0.010 mm/year in the placebo group and 0.012 mm/year in the testosterone group (mean difference adjusted for age and trial site, 0.0002 mm/year; 95% CI, -0.003 to 0.003, $P = .89$). End-of-treatment intima-media thickness did not differ sig-

nificantly between the 2 groups (mean, 0.90 mm; 95% CI, 0.86 to 0.94 testosterone and 0.92 mm; 95% CI, 0.88 to 0.96 placebo). The model-estimated 3-year change in common carotid artery intima-media thickness in participants who completed the intervention period did not differ significantly between groups (mean between-group difference, 0.005 mm; 95% CI, -0.004 to 0.014, $P = .30$) and was similar to that

Table. Baseline Characteristics of Participants

	Mean (SD)	
	Testosterone (n = 155)	Placebo (n = 151)
Trial site, No. (%)		
Charles R. Drew University	9 (5.8)	10 (6.6)
Kronos Longevity Research Institute	93 (60.0)	90 (59.6)
Boston Medical Center	53 (34.2)	51 (33.8)
Race, No. (%)		
Black	14 (10.4)	12 (9.1)
White	112 (83.0)	111 (84.1)
Age, y	66.9 (5.0)	68.3 (5.3)
Height, cm	175.3 (7.2)	175.4 (6.3)
Weight, kg	86.5 (11.0)	86.3 (10.7)
BMI	28.1 (2.9)	28.0 (2.9)
Risk factors, No. (%)		
Obese	40 (25.8)	42 (28.0)
Diabetes ^a	22 (14.2)	24 (16.0)
Hypertension ^a	71 (45.8)	57 (38.0)
Hyperlipidemia ^a	80 (51.6)	77 (51.3)
Medications, No. (%)		
Statins	68 (43.9)	65 (43.3)
Antihypertensive medication	51 (32.9)	41 (27.3)
Prior coronary artery disease, No. (%)	24 (15.5)	22 (14.7)
Total testosterone, ng/dL	307.2 (64.3)	307.4 (67.4)
≤200	186 (17.4)	165.3 (39.3)
No.	8	11
201-300	256.7 (30.1)	258.3 (30.0)
No.	62	51
>300	356.0 (34.6)	353.6 (31.0)
No.	84	88
Free testosterone, pg/mL	64.0 (17.2)	60.9 (18.0)
Estradiol, pg/mL	21.8 (14.9)	18.5 (10.0)
Sex hormone-binding globulin, μg/mL/L	3.1 (1.4)	3.2 (1.2)
Plasma, mg/dL		
Glucose	104.1 (23.3)	106.7 (25.7)
Total cholesterol	187.2 (42.1)	183.4 (36.7)
HDL cholesterol	47.1 (12.0)	48.7 (14.2)
LDL cholesterol	115.6 (35.2)	109.7 (31.9)
Triglycerides	142.7 (87.9)	138.9 (76.4)
Hemoglobin, g/dL	14.6 (1.2)	14.4 (1.6)
Hematocrit, %	43.7 (3.7)	43.6 (3.6)
Hemoglobin A _{1c} , %	5.7 (0.8)	5.7 (0.7)
PSA, ng/mL	1.31 (0.82)	1.25 (0.94)
Creatinine, mg/dL	1.06 (0.22)	1.06 (0.22)
CCA-IMT, mm	0.88 (0.21)	0.88 (0.20)
Coronary calcium, AU	452 (715)	508 (695)
Median (IQR)	142 (39-659)	148 (10-519)
0, No. (%)	21 (15.0)	20 (15.2)
1-100, No. (%)	42 (30.0)	32 (24.2)
101-300, No. (%)	26 (18.6)	27 (20.5)
>300, No. (%)	51 (36.4)	53 (40.2)

(continued)

Table. Baseline Characteristics of Participants (continued)

	Mean (SD)	
	Testosterone (n = 155)	Placebo (n = 151)
IPSS score ^b	6.6 (5.1)	7.2 (5.0)
Health-related QOL composite score, % ^c	81.5 (14.1)	83.4 (12.4)
Physical functioning, % ^d	89.9 (16.5)	90.4 (16.0)
IIEF composite score ^e	48.5 (21.1)	47.9 (22.2)
CARES score (marital subscale) ^f	3.7 (3.3)	3.7 (3.1)
Adherence, % ^g	94.6	94.8

Abbreviations: AU, Agatston units of coronary artery calcium; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CARES, Cancer Rehabilitation Evaluation System; CCA-IMT, common carotid artery intima-media thickness; HDL, high-density lipoprotein; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom score; LDL, low-density lipoprotein; PSA, prostate-specific antigen; QOL, quality of life.

SI conversion factors: To convert estradiol to pmol, multiply by 3.671; LDL, HDL, and total cholesterol to mmol/L, multiply by 0.0259; creatinine to μmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555; total testosterone to nmol/L, multiply by 0.0347; sex hormone-binding globulin to nmol/L, multiply by 8.896; and triglycerides to mmol/L, multiply by 0.0113.

^a Based on self-report or medication use.

^b Ranges from 0 (asymptomatic) to 35 (severely symptomatic).

^c Score range, 0% to 100%, with the highest representing perfect health-related QOL.

^d Self-reports of the physical function domain from the Medical Outcomes Study 36-item short form (range, 0%-100%), with highest score representing no dysfunction.

^e Score range, 0 to 75, with the highest representing no dysfunction.

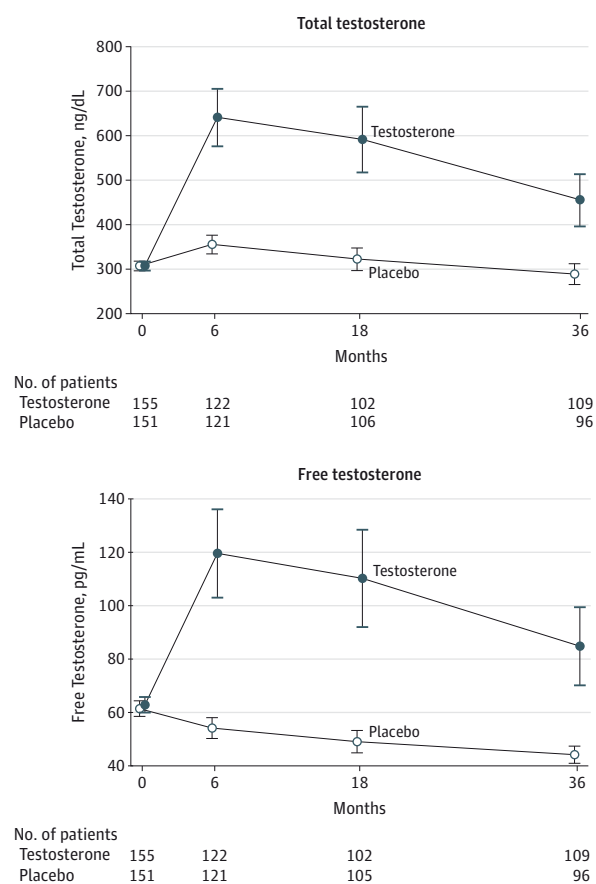
^f Score range, 0 to 24, with the highest representing most severe.

^g Medication adherence was determined by returned gel packets at follow-up visits.

obtained in the analysis of all 306 participants (eFigure 1 in [Supplement 4](#)). Among participants randomized to receive testosterone, changes in total or free testosterone levels were not significantly associated with change in intima-media thickness (eFigure 2 in [Supplement 4](#)).

Coronary Artery Calcium Scores

Baseline coronary artery calcium scores did not differ between groups. After adjustment for treatment site and age, the estimated per-year rate of change in coronary artery calcium during intervention was not significantly different between the 2 groups: 41.4 Agatston units/year in the placebo group and 31.4 Agatston units/year in the testosterone group (mean difference, −10.8; 95% CI, −45.7 to 24.2 Agatston units; $P = .54$; Figure 3). The model-estimated between-group difference in change from baseline to end-of-treatment coronary artery calcium in participants completing the intervention (mean difference, −24.3; 95% CI, −92.4 to 43.8; $P = .48$) was similar to the analysis involving all the participants, after adjustment for site and age (eFigure 1 in [Supplement 4](#)). Among participants randomized to receive testosterone, the changes in total or free testosterone were not significantly associated with changes in coronary artery calcium scores (eFigure 2 in [Supplement 4](#)).

Figure 2. Total and Free Testosterone Levels at Baseline and While Taking Study Medication

Means and 95% confidence intervals are presented as data markers and error bars.

Sexual Function

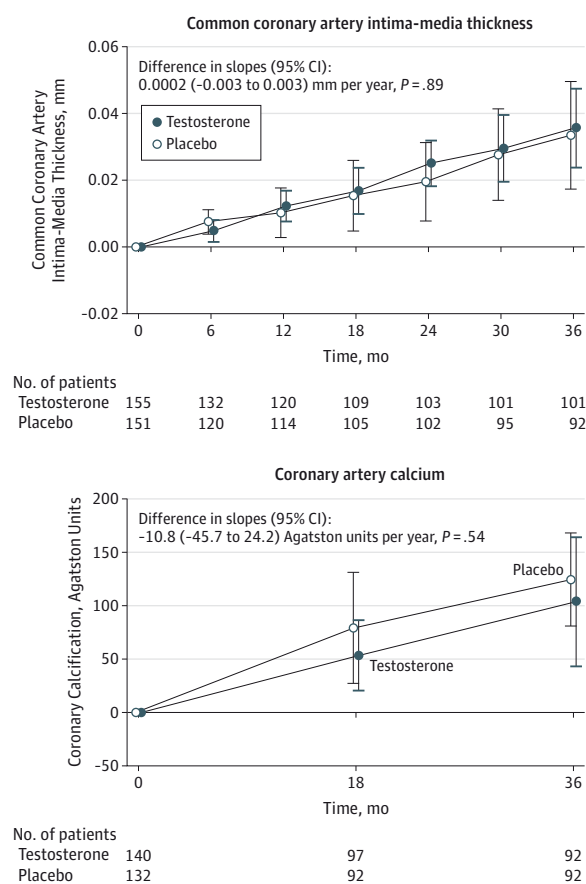
Exploratory assessments suggested nonlinear changes in most secondary outcomes with time; analyses therefore estimated differences between testosterone and placebo at postrandomization visits. The 2 groups did not differ significantly in the change from baseline in the composite IIEF score or in any domain scores (**Figure 4**). The intercourse satisfaction domain score improved significantly more in men in the testosterone group, but the improvements were modest (mean difference, 0.97; 95% CI, 0.0001-1.941; $P = .05$; **Figure 4**). There was no significant between-group difference in partner intimacy or interaction (**eFigure 3** in **Supplement 4**).

Health-Related QOL and Physical Functioning

Self-reported physical function, assessed using the physical function domain of the SF-36 did not differ significantly between groups (**eFigure 4** in **Supplement 4**). Neither the composite health-related QOL score nor any of the subdomain scores differed significantly between groups (**eFigure 5** in **Supplement 4**).

Serum Lipid and Blood Glucose Levels

The changes in total cholesterol, high-density lipoprotein, and low-density lipoprotein cholesterol; triglycerides; and fasting glucose levels did not differ between groups (**Figure 5**).

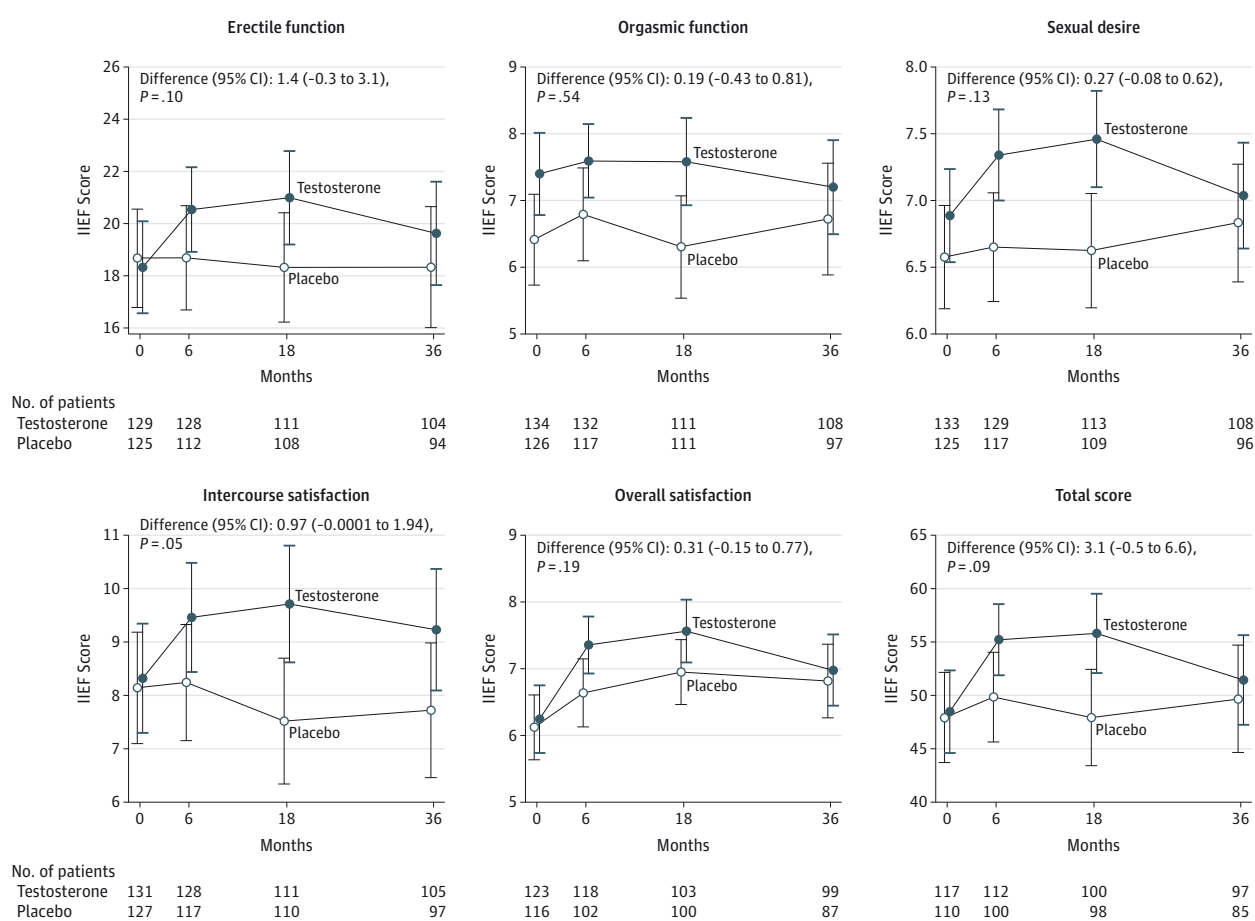
Figure 3. Change in Distal Common Carotid Artery Intima-Media Thickness and Coronary Artery Calcium Scores in Participants

The trajectory of change in carotid artery intima-media thickness and total coronary artery calcium by time since randomization. The means (data markers) and 95% CIs (error bars), generated from the observed data, are shown. Estimates are derived from mixed-effects regression models supplemented by multiple imputation of missing records (see the Methods section).

Sensitivity Analyses

We evaluated whether intervention effects varied according to baseline obesity status, diabetes status, or the presence of CAD at baseline (**eFigure 6** in **Supplement 4**). The rate of change in common carotid artery intima-media thickness or coronary artery calcium did not differ significantly between groups among men who were obese, had CAD, or had diabetes. Restricting the analyses to the 211 men who completed the 36-month intervention or stratifying the analyses by baseline coronary artery calcium (0, 1-49, >50 Agatston units) produced results similar to those obtained in the primary analysis. Analyses restricted to men with undetectable coronary artery calcium at baseline—all of whom were younger than 75 years—were similarly nonsignificant, with mean estimated between-group difference in per-year estimates 0.69 Agatston units (95% CI, -0.74 to 2.12). However, in a post hoc exploratory analysis of observed data restricted to statin non-users, the annual rate of change in coronary artery calcium was significantly lower in the testosterone group than in the placebo group (mean difference, -30.1; 95% CI, -59.1 to -1.0; $P = .04$). (**eFigure 6**, lower panel, in **Supplement 4**).

Figure 4. Sexual Function at Baseline and While Taking Study Medication



Each panel represents 1 of the 5 domains of the International Index of Erectile Function (IIEF). Means and 95% confidence intervals are presented as data markers and error bars. The mean estimated difference were derived while participants were taking the study medications (testosterone minus placebo);

estimates were derived from a mixed-effects regression model after adjusting for age group and study center, supported by multiple imputation of missing records (see the Methods section).

Adverse Events

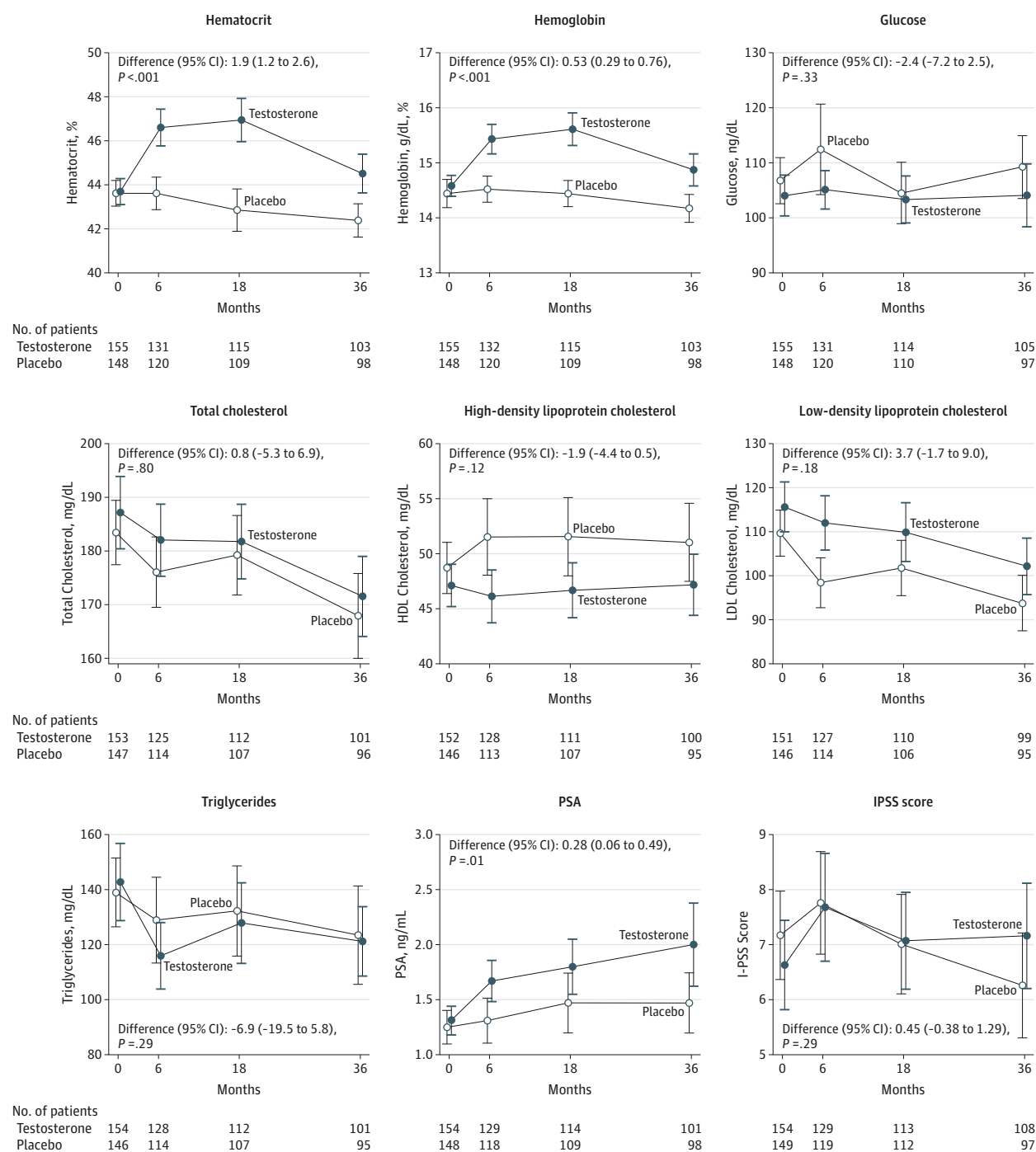
The number of participants reporting adverse events or serious adverse events did not differ between groups (eTable 2 in Supplement 2). Seventeen participants in the testosterone group experienced hematologic events vs 4 in the placebo group. Mean changes in hemoglobin (model-estimated mean difference, 0.53 g/dL; 95%CI, 0.29-0.76; $P < .001$) and hematocrit (model-estimated mean difference, 1.9%; 95% CI, 1.2%-2.6%; $P < .001$) were significantly greater in the testosterone group than in the placebo group (Figure 5). Thirteen men in testosterone group experienced hematocrit greater than 54% vs none in the placebo group. Four participants in the testosterone group, but none in the placebo group, experienced PSA levels greater than 4 ng/mL. Prostate-specific antigen levels increased significantly more in the testosterone group than in the placebo group (model-estimated mean difference, 0.28 ng/mL; 95% CI, 0.06-0.49; $P = .01$). Fourteen men in the testosterone group vs 2 in the placebo group had an IPSS score higher than 21; the IPSS score change was greater in the testosterone group, but the model-estimated mean difference was

0.45 (95% CI, -0.4 to 1.3; $P = .29$; Figure 5) was not statistically significant. The small number of adjudicated CVD events and major adverse cardiovascular events did not differ between groups: 3 in the testosterone vs 2 in the placebo group had myocardial infarction; 5 in the testosterone vs 2 in the placebo group had undergone coronary revascularization; 3 in the testosterone vs 0 in the placebo group had had a stroke, and 1 in the testosterone group vs 0 in the placebo group had died of a cardiovascular-related event.

Discussion

The rates of subclinical atherosclerosis progression in community-dwelling older men with low or low-normal testosterone levels did not differ significantly between men assigned to the testosterone or placebo groups. The results obtained using either marker of atherosclerosis were concordant in demonstrating no significant association between randomization to testosterone and the rates of intima-media thickness progression or

Figure 5. Safety and Laboratory Assessments: Baseline and On-treatment Analytes and International Prostate Symptom Score



Means and 95% confidence intervals are presented as data markers and error bars. The mean estimated difference (testosterone minus placebo) were derived while participants were taking the study medication; estimates were derived from a mixed-effects regression model after controlling for age and

study center, supported by multiple imputation of missing records (see the Methods section). PSA indicates prostate-specific antigen; IPSS, International Prostate Symptom Score.

change in coronary artery calcium scores. Sensitivity analyses involving men with diabetes or obesity who were in various categories of calcium scores or who had completed the 3-year intervention were consistent with results obtained in the overall intention-to-treat population. These findings were

further corroborated by the lack of significant association between the change in testosterone levels and change from baseline in either intima-media thickness or calcium scores. In CLAS,^{24,25} for each 0.03-mm increase in intima-media thickness, the relative risk of nonfatal myocardial infarction or coro-

nary death was 2.2 and risk of any coronary artery disease event was 3.3. Thus, the trial was adequately powered to detect clinically meaningful between-group differences that were even smaller than those observed with cholesterol-lowering therapy. The observed differences between groups were neither statistically significant nor clinically meaningful.

Testosterone administration did not significantly improve erectile or ejaculatory function, sexual desire, partner intimacy, or health-related QOL. The improvements in intercourse satisfaction, although statistically significant, were of small magnitude and could be due to chance alone, in light of the lack of improvements in other domains of sexual function. Thus, the effects of testosterone on sexual function in this population contrast with those of phosphodiesterase inhibitors, which are associated with substantial improvements in erectile function, orgasmic function, intercourse satisfaction, and overall satisfaction in men with erectile dysfunction.²⁶ These data are consistent with the results of meta-analyses of testosterone trials, which have also reported no significant improvements in sexual function in men who have normal or low-normal testosterone levels.^{27,28} Dose-response studies²⁹⁻³¹ and randomized trials involving men with low-normal testosterone levels have suggested that increasing testosterone levels above the lower limit of the normal range in healthy men does not further improve sexual function. It is possible that testosterone supplementation may improve measures of sexual function in older men with unequivocally low testosterone levels, as has been suggested by several meta-analyses.^{27,28}

The trial had many strengths—inclusion of a placebo control, parallel-group design, double-blinding, concealed randomization, and intention-to-treat analytic strategy. To our knowledge, this is the largest randomized trial investigating testosterone's effects on atherosclerosis progression in older men to date. The ongoing T Trials, a coordinated set of 7 trials, includes a substudy of testosterone's effects on plaque volume over 1 year among approximately 140 men³²; those data, when available, will provide important complementary information to the data reported herein. The TEAAM trial's 3-year intervention duration was sufficiently long to determine clinically meaningful effects of the intervention on common carotid artery intima-media thickness and coronary artery calcium. During the trial, the testosterone dose was adjusted to maintain testosterone levels at the mid-normal range. The testosterone threshold used for inclusion in the trial was similar to that used in some trials but higher than that used in other trials.³³⁻³⁸ The testosterone dose in the trial may be higher than that used typically in clinical practice and in some trials but was not dissimilar from that used in other trials.^{2,3,33-38} We aimed to maintain the average testosterone concentrations in the testosterone group at the mid-normal range established for young men, consistent with the Endocrine Society's guideline² for testosterone therapy and was not different from levels reported in other trials.^{3,33-39} However, testosterone levels declined over time in men assigned to the testosterone group; this could be due to treatment adherence being less than that reported by the participants, due to changes in testosterone metabolism over time, or due

to progressive suppression of endogenous testosterone production with continued testosterone administration. Two different markers of atherosclerosis provided consistent results.

The trial had several limitations that could affect the generalizability of these findings. The loss-to-follow-up rate was high but was not dissimilar from that observed in other trials of comparable duration^{36,40} and was substantially better than that observed in clinical practice.^{41,42} The participants who were lost to follow-up did not differ from those who stayed in the trial. The recruitment was unequal across trial sites. The effectiveness of participant blinding was not assessed. *P* values were not adjusted for multiple comparisons, which may increase the risk of false rejection of null hypothesis (eg, in the case of intercourse satisfaction). These men were not selected based on a diagnosis of hypogonadism or symptoms of hypogonadism and some men included in the trial had low-normal testosterone levels, similar to men included in many previous trials involving older men³³⁻³⁷ and to many older men receiving testosterone therapy in clinical practice.⁴² These findings should not be extrapolated to men with classical hypogonadism due to known diseases of the testis, pituitary, and the hypothalamus. Testosterone levels were measured using an immunoassay because LC-MS/MS assays were not available at the time of trial's initiation. The trial, which was powered for atherosclerosis progression, had limited statistical power for sensitivity analyses conducted in smaller subgroups. Although measures of subclinical atherosclerosis have been shown to be predictive of cardiovascular events,^{13-15,24,25,43} the changes in these subclinical measures with various interventions have correlated with changes in CVD event rates in some trials but not others. Coronary artery calcium only measures calcified plaque and some intervention trials did not show a significant change in calcium progression in spite of changes in cardiovascular events.

The TEAAM trial was not designed to determine the effects of testosterone on CVD events, which were not adjudicated or ascertained using a structured instrument. A substantially larger trial would be needed to determine testosterone's effects on CVD events. Although numerically there were more CVD events among men assigned to the testosterone group than to the placebo group, CVD events were sparse and not adjudicated. The TEAAM trial's study population differed from that enrolled in the Testosterone in Older Men with Mobility Limitation (TOM) trial,³ which was stopped early due to a higher frequency of cardiovascular events in the testosterone group than in the placebo group. The participants in the TEAAM trial were, in general, younger, healthier, and not mobility limited and had lower baseline prevalence of cardiovascular risk factors than those in the TOM trial. The TEAAM trial's findings suggest that the observed increase in cardiovascular events in the TOM trial and in some retrospective analyses cannot be attributed to testosterone's effects on atherosclerosis progression. Also, CVD events in the TOM trial³ and the study by Finkel et al⁴ occurred early in the course of testosterone administration. It is possible that testosterone may affect plaque stability, clot formation, salt and water retention, inflammation, or other

mechanisms that might render some men susceptible to early CVD events. The findings of this randomized trial differ from those of some epidemiological studies, which have reported low testosterone levels to be associated with higher common carotid artery intima-media thickness.^{2,11} Low testosterone levels have also been reported in some studies to be associated with cardiovascular and all-cause mortality.⁹ Similar differences in the results of epidemiological studies and randomized trials have been observed for estrogen therapies for women. The differences in the effects of endogenous circulating hormones in contrast to those of exogenously administered hormonal therapies as well as variable at-risk timeframes could contribute to the apparent discrepancies between epidemiological and randomized trial results. In epidemiological studies, reverse causality cannot be excluded. Those at higher risk of death might have low testosterone levels due to illness or other factors that contribute to higher mortality.

In exploratory analyses, among statin nonusers, the rate of change in coronary artery calcium was lower in the testosterone group than in the placebo group; the opposite was found in statin users. These findings are similar to those reported in estradiol trials in postmenopausal women, in which estradiol's effects on atherosclerosis were more strikingly apparent in statin nonusers than in statin users.¹⁴ Statin

use is a marker of increased cardiovascular risk, and it is possible that the effects of testosterone may differ in older men at high risk of CVD. It is also possible that statin use masked a potentially beneficial effect of testosterone on atherosclerosis progression. This post hoc exploratory analysis was neither prespecified nor adjusted for multiple comparisons. Additional trials should investigate the hypothesis suggested by these exploratory analyses of whether testosterone retards atherosclerosis progression in older men who are not using statins.

Conclusions

Among older men with low or low-normal testosterone levels, testosterone administration for 3 years compared with placebo did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium nor was it associated with improved overall sexual function or health-related QOL. Because this trial was only powered to evaluate atherosclerosis progression and not cardiovascular events, these findings should not be interpreted as establishing cardiovascular safety of testosterone use in older men such as those enrolled in this trial.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: All the authors.

Drafting of the manuscript: Basaria, Harman, Travison, Pencina, Bhasin.

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Administrative, technical, or material support: Hodis, Tsitouras, Budoff, Coviello, Knapp, Hally, Pinjic, Yan, Bhasin.

Study supervision: Basaria, Harman, Hodis, Tsitouras, Budoff, Dzekov, Mazer, Storer, Bhasin.

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Data and Safety Monitoring Board: Thomas T. Yoshikawa, MD, (chair), Charles R. Drew University; William French, MD, Harbor-UCLA Medical Center; Nand Datta, MD, Charles R. Drew University, none of whom were compensated.

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REFERENCES

- 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.
- 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.
- Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med.* 2010;363(2):109-122.
- 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.
- 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.
- 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.
- Bhasin S, Jasjua GK, Pencina M, et al. Sex hormone-binding globulin, but not testosterone, is associated prospectively and independently with incident metabolic syndrome in men: the framingham heart study. *Diabetes Care.* 2011;34(11):2464-2470.
- Muller M, van der Schouw YT, Thijssen JH, Grobbee DE. Endogenous sex hormones and cardiovascular disease in men. *J Clin Endocrinol Metab.* 2003;88(11):5076-5086.
- Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2011;96(10):3007-3019.
- Barrett-Connor E, Khaw KT. Endogenous sex hormones and cardiovascular disease in men: a prospective population-based study. *Circulation.* 1988;78(3):539-545.
- Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SW, van der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation.* 2004;109(17):2074-2079.
- Nathan L, Shi W, Dinh H, et al. Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. *Proc Natl Acad Sci U S A.* 2001;98(6):3589-3593.
- Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med.* 1998;128(4):262-269.
- Hodis HN, Mack WJ, Lobo RA, et al; Estrogen in the Prevention of Atherosclerosis Trial Research Group. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2001;135(11):939-953.
- Budoff MJ, Young R, Lopez VA, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol.* 2013;61(12):1231-1239.
- Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med.* 2014;161(4):249-260.
- Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology.* 1997;49(6):822-830.
- Paige NM, Hays RD, Litwin MS, Rajfer J, Shapiro MF. Improvement in emotional well-being and relationships of users of sildenafil. *J Urol.* 2001;166(5):1774-1778.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36), I: Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.
- Salameh WA, Redor-Goldman MM, Clarke NJ, Reitz RE, Caulfield MP. Validation of a total testosterone assay using high-turbulence liquid chromatography tandem mass spectrometry: total and free testosterone reference ranges. *Steroids.* 2010;75(2):169-175.
- Bhasin S, Travison TG, Storer TW, et al. Effect of testosterone supplementation with and without a dual 5 α -reductase inhibitor on fat-free mass in men with suppressed testosterone production: a randomized controlled trial. *JAMA.* 2012;307(9):931-939.
- Mazer NA. A novel spreadsheet method for calculating the free serum concentrations of testosterone, dihydrotestosterone, estradiol, estrone and cortisol: with illustrative examples from male and female populations. *Steroids.* 2009;74(6):512-519.
- Van Buuren S, Groothuis-Oudshoorn K. *Multivariate Imputation by Chained Equations: MICE V1.0 User's Manual.* Leiden, the Netherlands: TNO Quality of Life; 2000.
- Blankenhorn DH, Selzer RH, Crawford DW, et al. Beneficial effects of colestipol-niacin therapy on the common carotid artery: two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation.* 1993;88(1):20-28.
- Hodis HN, Mack WJ, LaBree L, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med.* 1996;124(6):548-556.
- Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA; Sildenafil Study Group. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med.* 1998;338(20):1397-1404.
- Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J Urol.* 2000;164(2):371-375.
- Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol (Oxf).* 2005;63(4):381-394.
- Buena F, Swerdloff RS, Steiner BS, et al. Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. *Fertil Steril.* 1993;59(5):1118-1123.
- Grey PB, Singh AB, Woodhouse L, et al. Dose-dependent effects of testosterone on sexual function in older men. *J Clin Endocrinol Metab.* 2005;90:3838-3846.
- Finkelstein JS, Lee H, Burnett-Bowie SA, et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med.* 2013;369(11):1011-1022.
- Snyder PJ, Ellenberg SS, Cunningham GR, et al. The Testosterone Trials: seven coordinated trials of testosterone treatment in elderly men. *Clin Trials.* 2014;11(3):362-375.
- Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab.* 1999;84(8):2647-2653.
- Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *JAMA.* 2008;299(1):39-52.
- Nair KS, Rizza RA, O'Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med.* 2006;355(16):1647-1659.
- Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab.* 2005;90(3):1502-1510.
- 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.
- Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA.* 2006;296(19):2351-2361.
- 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.
- Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333.
- Schoenfeld MJ, Shortridge E, Cui Z, Muram D. Medication adherence and treatment patterns for hypogonadal patients treated with topical testosterone therapy: a retrospective medical claims analysis. *J Sex Med.* 2013;10(5):1401-1409.
- Jasuja GK, Bhasin S, Reisman JL, Rose AJ. Wide variations in the use of testosterone therapy among VA facilities. *Am J Pharm Benefits.* 2013;5(5):e122-e128.
- Budoff MJ, Lane KL, Bakhsheshi H, et al. Rates of progression of coronary calcium by electron beam tomography. *Am J Cardiol.* 2000;86(1):8-11.