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# Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone

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**IMPORTANCE** Recent studies have yielded conflicting results as to whether testosterone treatment increases cardiovascular risk.

**OBJECTIVE** To test the hypothesis that testosterone treatment of older men with low testosterone slows progression of noncalcified coronary artery plaque volume.

**DESIGN, SETTING, AND PARTICIPANTS** Double-blinded, placebo-controlled trial at 9 academic medical centers in the United States. The participants were 170 of 788 men aged 65 years or older with an average of 2 serum testosterone levels lower than 275 ng/dL (82 men assigned to placebo, 88 to testosterone) and symptoms suggestive of hypogonadism who were enrolled in the Testosterone Trials between June 24, 2010, and June 9, 2014.

**INTERVENTION** Testosterone gel, with the dose adjusted to maintain the testosterone level in the normal range for young men, or placebo gel for 12 months.

**MAIN OUTCOMES AND MEASURES** The primary outcome was noncalcified coronary artery plaque volume, as determined by coronary computed tomographic angiography. Secondary outcomes included total coronary artery plaque volume and coronary artery calcium score (range of 0 to >400 Agatston units, with higher values indicating more severe atherosclerosis).

**RESULTS** Of 170 men who were enrolled, 138 (73 receiving testosterone treatment and 65 receiving placebo) completed the study and were available for the primary analysis. Among the 138 men, the mean (SD) age was 71.2 (5.7) years, and 81% were white. At baseline, 70 men (50.7%) had a coronary artery calcification score higher than 300 Agatston units, reflecting severe atherosclerosis. For the primary outcome, testosterone treatment compared with placebo was associated with a significantly greater increase in noncalcified plaque volume from baseline to 12 months (from median values of 204 mm<sup>3</sup> to 232 mm<sup>3</sup> vs 317 mm<sup>3</sup> to 325 mm<sup>3</sup>, respectively; estimated difference, 41 mm<sup>3</sup>; 95% CI, 14 to 67 mm<sup>3</sup>; *P* = .003). For the secondary outcomes, the median total plaque volume increased from baseline to 12 months from 272 mm<sup>3</sup> to 318 mm<sup>3</sup> in the testosterone group vs from 499 mm<sup>3</sup> to 541 mm<sup>3</sup> in the placebo group (estimated difference, 47 mm<sup>3</sup>; 95% CI, 13 to 80 mm<sup>3</sup>; *P* = .006), and the median coronary artery calcification score changed from 255 to 244 Agatston units in the testosterone group vs 494 to 503 Agatston units in the placebo group (estimated difference, -27 Agatston units; 95% CI, -80 to 26 Agatston units). No major adverse cardiovascular events occurred in either group.

**CONCLUSIONS AND RELEVANCE** Among older men with symptomatic hypogonadism, treatment with testosterone gel for 1 year compared with placebo was associated with a significantly greater increase in coronary artery noncalcified plaque volume, as measured by coronary computed tomographic angiography. Larger studies are needed to understand the clinical implications of this finding.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: [NCT00799617](https://clinicaltrials.gov/ct2/show/study/NCT00799617)

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Although testosterone replacement is increasingly being used clinically,<sup>1</sup> the cardiovascular benefits and risks of testosterone administration to older men with age-related decline in testosterone levels remain uncertain. Several observational studies show an inverse association between serum testosterone concentration and adverse cardiovascular outcomes, the metabolic syndrome, diabetes, and mortality,<sup>2-5</sup> independent of traditional cardiovascular risk factors.

Studies of the effects of testosterone on clinical cardiovascular outcomes are conflicting.<sup>6</sup> Meta-analyses of clinical trials have shown no association between testosterone treatment and cardiovascular adverse events, but none of the individual trials included in the meta-analyses were designed to assess these events prospectively. A clinical trial in older men with mobility limitation showed an excess of cardiovascular adverse events in men treated with testosterone compared with placebo,<sup>7</sup> but another trial in a similar population did not.<sup>8</sup> These trials were also not designed to assess cardiovascular adverse events. Retrospective analyses of electronic medical records to evaluate the possible association of testosterone treatment with cardiovascular adverse events have also yielded conflicting results.<sup>9-13</sup>

The Testosterone Trials (TTrials), a group of 7 placebo-controlled, coordinated trials, were designed to determine the efficacy of testosterone treatment of men aged 65 years or older with low testosterone concentrations for no apparent reason other than age. The Cardiovascular Trial was designed to test the hypothesis that testosterone treatment of older men with low testosterone slows the progression of noncalcified coronary artery plaque volume, assessed by coronary computed tomographic angiography (CCTA), as an indicator of coronary atherosclerosis.

## Methods

### Study Design

The overall study design of the TTrials<sup>14</sup> as well as the design of the Cardiovascular Trial<sup>15</sup> have been published. To qualify for the TTrials overall, a participant had to qualify for at least 1 of the 3 main trials (Sexual Function Trial, Physical Function Trial, and Vitality Trial). Those who qualified overall could participate in any of the others for which they qualified. Participants were allocated to receive testosterone or placebo gel for 1 year. This article describes the results of the Cardiovascular Trial.

The TTrials and the Cardiovascular Trial protocols were approved by the institutional review boards of the participating sites. The trial protocols for the TTrials and the Cardiovascular Trial are available in [Supplement 1](#). All participants provided written informed consent. Participant safety and trial conduct were overseen by an independent data and safety monitoring board.

### Participants

Participants were recruited primarily by mass mailings.<sup>16</sup> Respondents were screened by telephone and then during 2 clinic

## Key Points

**Question** Is testosterone treatment of older men with low testosterone associated with a decrease in noncalcified coronary artery plaque volume?

**Findings** In a controlled clinical trial, 1 year of testosterone treatment of men aged 65 years or older with a low serum testosterone level was associated with a significant increase in noncalcified coronary artery plaque volume of 41 mm<sup>3</sup> more than placebo.

**Meaning** Testosterone treatment of older men was associated with an increase in coronary artery plaque volume, but additional studies are needed to determine the clinical significance.

visits. The main overall inclusion criteria were men aged 65 years or older, serum testosterone levels that averaged lower than 275 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) on 2 morning samples, and subjective complaints and objective evidence of sexual dysfunction, physical dysfunction, and/or reduced vitality. The main exclusion criterion was high risk of prostate cancer.<sup>14</sup> Men who had a history of myocardial infarction or stroke within the previous 3 months and who had a systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 100 mm Hg were excluded.

Additional exclusion criteria for the Cardiovascular Trial were related to CCTA: conditions that either increased the risk of performing the procedure (estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup> or known allergy to iodinated contrast medium) or made the procedure technically impractical (weight >136 kg, inability to hold the breath for 10 seconds, a prior diagnosis of tachycardia or irregular heart rhythm [eg, atrial fibrillation], or history of coronary artery bypass graft surgery). Self-report of race and ethnicity, by fixed categories, was collected as required by the National Institutes of Health.

### Testosterone Treatment

Participants were allocated to treatment by minimization, a computerized allocation technique that calculates the assignment that provides the best balance across groups on specified baseline characteristics. A random component was included by assigning the optimally balancing treatment with 80% probability.<sup>14</sup> The balancing variables included participation in the main trials, trial site, age younger than or older than 75 years, screening testosterone concentration lower than or higher than 200 ng/dL, and use of antidepressants and phosphodiesterase type 5 (PDE5) inhibitors.<sup>14</sup> There was only 1 treatment assignment that applied to all trials in which a man participated.

Testosterone was administered as a 1% gel in a pump bottle (AndroGel). Placebo gel was similar. The dose was initially 5 g/d and was adjusted, if necessary, on the basis of testosterone levels measured at a central laboratory (Quest Clinical Trials) at months 1, 2, 3, 6, and 9, to try to keep the serum concentration within the normal range for young men (280-873 ng/dL). To maintain blinding when the dose was adjusted in a man receiving testosterone treatment, the dose was changed simultaneously in a man receiving placebo.

## Assessments

The concentrations of testosterone, free testosterone, and estradiol were measured on serum samples drawn at baseline and months 3, 6, 9, and 12 and stored at  $-80^{\circ}\text{C}$ . These assays were performed at the Brigham Research Assay Core as previously described.<sup>17</sup>

Coronary artery plaque volume was assessed by CCTA at 9 of the 12 TTrials clinical sites. Each of these sites had at least a 64-slice CCTA scanner and staff experienced in CCTA, as determined by a questionnaire.<sup>15</sup> Precontrast scans for evaluation of coronary artery calcium density and postcontrast scans for evaluation of coronary artery plaque volume were performed at baseline and 12 months. If a participant who had a baseline scan developed an allergy to contrast medium or experienced a decrease in estimated glomerular filtration rate to 60 mL/min/1.73 m<sup>2</sup> or less before the month 12 scan, only the precontrast scan was performed at month 12.

All scans were evaluated at a central reading center (Harbor-UCLA Medical Center) by an investigator blinded to treatment assignment. Coronary images were transferred to the workstation with the use of semiautomated plaque analysis software (QAngioCT Research Edition Version 2.0.5; Medis Medical Imaging Systems) and evaluated using a protocol for quantitative plaque assessment.<sup>18,19</sup> Vessel diameters greater than 1.5 mm were evaluated and assessed based on a Society of Cardiovascular Computed Tomography 17-segment coronary artery model.<sup>20</sup>

The readers (R.N., N.N., and S.M.), blinded to both treatment group and date of scan, evaluated the baseline and month 12 scans side by side to ensure that the same segments were compared and measured. The area of each coronary plaque visualized in at least 2 adjacent slices (reconstructed slice thickness of 0.6 mm) was determined on all affected slices. The total plaque volume per segment was summed over all segments with plaque. In addition, each coronary territory (right coronary artery, left main artery, left anterior descending artery, and left circumflex artery) was scored according to presence of the most significant lesion.

The volumes of 4 types of coronary artery plaque—low attenuation, fibrous-fatty, fibrous, and dense calcium—were calculated by the Hounsfield unit threshold. The Hounsfield unit threshold was changed dynamically by the software, as plaque attenuation values are affected by luminal contrast densities.<sup>21</sup> The primary outcome was noncalcified plaque volume, defined as the sum of the low attenuation, fibrous-fatty, and fibrous plaque volumes. (The primary outcome was originally [October 2010] total plaque volume but was changed to noncalcified plaque volume in the final protocol of October 2012 [Supplement 1]. Determination of plaque volume was not made until all participants had completed the trial in June 2014.) The secondary outcomes were (1) total plaque volume, defined as the sum of the volume of all 4 types of coronary artery plaque volume (low attenuation, fibrous-fatty, fibrous, and dense calcium); and (2) coronary artery calcium score. The exploratory outcomes were the 4 individual components of plaque volume.

Reproducibility of the coronary artery plaque volume readings in the reading center was assessed by dividing the

analyzed scans into quartiles based on noncalcified plaque volume and selecting 10 scans from each quartile to ensure representation of the full range of plaque volumes. One original reader read each of the 40 scans once, and a new reader read each twice, a week apart and in a different order. Intraobserver and interobserver reliability for the primary outcome of noncalcified plaque volume was assessed using linear regression and Bland-Altman plots. The intraclass correlations (ICCs) and coefficients of variation (CVs) were also calculated. For noncalcified plaque volume, the intraobserver CV was 7.8%, the intraobserver ICC was 0.99, the interobserver CV was 19.9%, and the interobserver ICC was 0.95. The intraobserver and interobserver variability was greater for some of the individual plaque components. Details are provided in the eAppendix, eFigure 1, eFigure 2, and eTable 1 in Supplement 2.

Coronary artery calcium score, a secondary outcome, was determined on precontrast scans as previously described.<sup>22</sup>

## Statistical Analyses

The association of testosterone with outcomes related to coronary artery plaque and calcium scores was assessed using a multivariable linear model that adjusted for baseline plaque volume and all balancing variables used in the minimization procedure: study site, indicator variables of participation in each primary efficacy trial, baseline testosterone concentration ( $\leq 200$  ng/dL or  $>200$  ng/dL), age ( $\leq 75$  years or  $>75$  years), use of antidepressants, and use of PDE5 inhibitors as covariables. The adjusted mean difference was calculated for the change in plaque volume from baseline to month 12 for men allocated to testosterone compared with placebo. All participants with measurements of both baseline and 12-month plaque volumes were included in the analysis. Significance of the association between testosterone treatment and plaque volume was assessed using the 2-sided Wald test and 95% confidence interval. Assessment of the association of the use of statins and assessment of change in testosterone, free testosterone, and estradiol levels with change in plaque volume for men assigned to testosterone treatment were done by regression analysis, adjusting for balancing variables and baseline plaque volume. A sensitivity analysis to assess the potential effect of missing data was performed by multiple imputation with all known and measured risk factors for cardiovascular disease (age; body mass index [calculated as weight in kilograms divided by height in meters squared]; smoking status; diabetes; hypertension; prior myocardial infarction; prior stroke; revascularization; sleep apnea; use of medications for diabetes, hypertension, or lipid lowering; baseline plaque volumes; and baseline testosterone level) in addition to the balancing factors used to develop the model. The Markov chain Monte Carlo method was used to impute the missing values under the assumption of an arbitrary missing pattern. No adjustments were made for multiple testing. All hypothesis testing used a 2-sided  $P = .05$  significance threshold. All analyses were performed using SAS version 9.4 statistical software (SAS Institute Inc).

The sample size for this trial was initially estimated to be 400 men in the protocol of October 2010 but was

later reduced to 140 men when the primary outcome was changed from total to noncalcified plaque volume, because the latter has a smaller standard deviation.<sup>23</sup> Using a standard deviation of 26 mm<sup>3</sup> for the change in volume from scans obtained at 2 time points approximately 1 year apart in that study, 140 men (70 per group) with both baseline and month 12 scans would provide 80% power to detect a difference of 12 mm<sup>3</sup> in the change in noncalcified plaque volume from baseline to 12 months (protocol of October 2012, [Supplement 1](#)). This difference was chosen to be smaller than the 14- to 15-mm<sup>3</sup> difference seen between statin users and nonusers.<sup>23</sup>

## Results

### Participants

Recruitment began on April 28, 2011. Targeted enrollment was completed on June 11, 2013, and treatment was completed on June 16, 2014. Of the 460 men enrolled in the TTrials at the 9 sites participating in the Cardiovascular Trial, 170 consented and enrolled, and 166 had a baseline scan, 86 in the testosterone group and 80 in the placebo group ([Figure](#)). A total of 138 men had a month 12 scan, 73 in the testosterone group and 65 in the placebo group, that could be analyzed. Nine men in the testosterone group and 11 men in the placebo group did not have month 12 scans even though they were still enrolled, because they either developed a reason for exclusion or refused to have the second scan. [eTable 2 in Supplement 2](#) shows the numbers of men in this trial who participated in the 3 main trials of the TTrials.

At baseline, the mean (SD) age was 71.2 (5.7) years, and 81% were white. The participants had relatively high rates of obesity and concomitant illnesses, such as hypertension, hyperlipidemia, and diabetes, as well as relatively high 10-year risk of a cardiovascular event by the American College of Cardiology/American Heart Association risk calculator<sup>24</sup> (a mean risk of 24% [95% CI, 2.6%-45.4%] in the testosterone group and 27% [95% CI, 6.4%-47.6%] in the placebo group) ([Table 1](#)). The prevalence of atherosclerosis, assessed radiographically by a coronary artery calcification score higher than 300 Agatston units, was also high (70 men [50.7%] overall; 60.3% in the placebo group and 43.8% in the testosterone group).

Testosterone treatment increased the serum testosterone concentrations from unequivocally low to midnormal for young men by month 3 and maintained that level through month 12 ([eFigure 3 in Supplement 2](#)). Testosterone treatment also increased the levels of free testosterone and estradiol to midnormal for young men.

### CCTA and Coronary Artery Calcium Results

At baseline, noncalcified plaque volume showed considerable variability, and the median in the testosterone group (204 mm<sup>3</sup> [interquartile range, 60 to 420 mm<sup>3</sup>]) was somewhat lower than that in the placebo group (317 mm<sup>3</sup> [interquartile range, 168 to 589 mm<sup>3</sup>]) ([Table 2](#)). The components of noncalcified plaque volume (low-attenuation plaque,

fibrous-fatty plaque, and fibrous plaque) and total plaque volume (noncalcified plaque plus dense calcium plaque) were also somewhat lower in the testosterone group ([Table 2](#)).

For the primary outcome, noncalcified coronary artery plaque volume, testosterone treatment was associated with a significantly greater increase from baseline to month 12 (from median of 204 mm<sup>3</sup> to 232 mm<sup>3</sup>; change: mean, 40 mm<sup>3</sup>; 95% CI, 23 to 56 mm<sup>3</sup>) than placebo (from median of 317 mm<sup>3</sup> to 325 mm<sup>3</sup>; change: mean, 4 mm<sup>3</sup>; 95% CI, -14 to 22 mm<sup>3</sup>) (estimated difference, 41 mm<sup>3</sup>; 95% CI, 14 to 67 mm<sup>3</sup>; *P* = .003) ([Table 2](#)). Sensitivity analysis using multiple imputation to account for missing data resulted in similar point estimates, and confidence intervals were almost identical (estimated difference, 39 mm<sup>3</sup>; 95% CI, 13 to 65 mm<sup>3</sup>). The *P* value for the difference in plaque volume in this analysis was .003.

For the secondary outcome of total plaque volume, testosterone was significantly associated with a greater increase from baseline to month 12 (from a median of 272 mm<sup>3</sup> to 318 mm<sup>3</sup>; change: mean, 57 mm<sup>3</sup>; 95% CI, 35 to 78 mm<sup>3</sup>) than placebo (from a median of 499 mm<sup>3</sup> to 541 mm<sup>3</sup>; change: mean, 21 mm<sup>3</sup>; 95% CI, 0 to 42 mm<sup>3</sup>) (estimated difference, 47 mm<sup>3</sup>; 95% CI, 13 to 80 mm<sup>3</sup>; *P* = .006). For the secondary outcome of coronary artery calcium score, testosterone was not statistically significantly associated with a change from baseline to 12 months (change in testosterone group: mean, 53 Agatston units; 95% CI, 25 to 82 Agatston units; change in placebo group: mean, 118 Agatston units; 95% CI, 73 to 164 Agatston units). The median scores changed from 255 to 244 Agatston units in the testosterone group vs 494 to 503 Agatston units in the placebo group (estimated difference, -27 Agatston units; 95% CI, -80 to 26 Agatston units; *P* = .31).

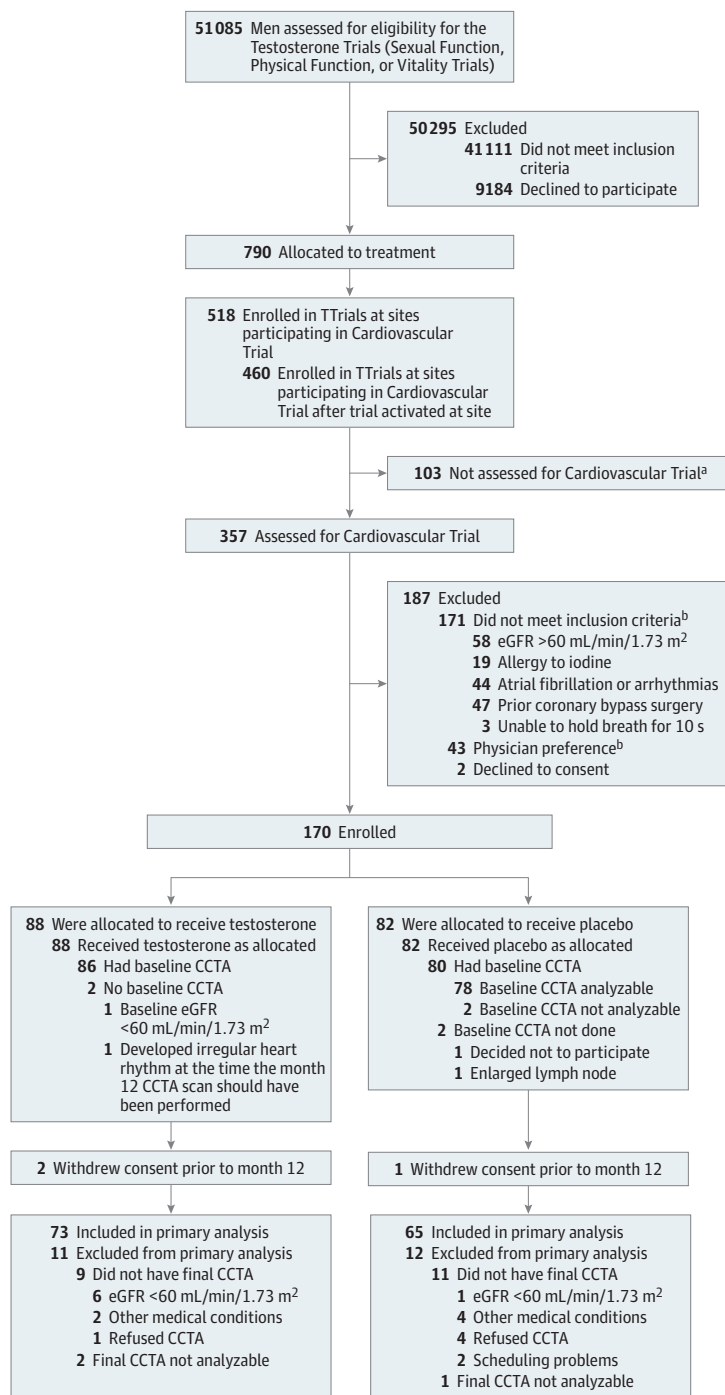
Exploratory analyses of the individual components of noncalcified plaque showed that testosterone treatment was associated with a significantly greater increase in fibrous plaque volume (change, 25 mm<sup>3</sup>; 95% CI, 14 to 35 mm<sup>3</sup>) than placebo (change, 1 mm<sup>3</sup>; 95% CI, -13 to 15 mm<sup>3</sup>) (estimated difference, 24 mm<sup>3</sup>; 95% CI, 5 to 43 mm<sup>3</sup>; *P* = .01) ([Table 2](#)). Testosterone was also associated with greater increases in low-attenuation plaque volume and fibrous-fatty plaque volume, but neither difference reached statistical significance. Testosterone and placebo were associated with almost identical (and not statistically significant) changes in dense calcium plaque volume.

The change in noncalcified coronary artery plaque volume in men in the testosterone group was not associated with changes in levels of total testosterone (*r* = -0.04; *P* = .74), free testosterone (*r* = -0.006; *P* = .96), or estradiol (*r* = -0.08; *P* = .50). The changes were also not associated with statin use (*P* = .35). Differences in plaque volume were similar for men with baseline coronary artery calcium scores higher and lower than the median value.

### Adverse Events

Among the 170 men enrolled in the Cardiovascular Trial, none in either the testosterone treatment group or the placebo group were reported to have a major adverse cardiovascular event.

Figure. Screening and Retention of Participants in the Cardiovascular Trial



CCTA indicates coronary computed tomographic angiography; eGFR, estimated glomerular filtration rate; and TTrial, Testosterone Trial.

<sup>a</sup> Reasons unknown; no assessment form submitted.

<sup>b</sup> Some men had more than 1 reason.

## Discussion

One year of testosterone treatment of men aged 65 years or older with low testosterone was associated with an increase in noncalcified coronary artery plaque volume, as determined by CCTA. Testosterone treatment was also associated with increased total plaque volume, but not with changes in coronary artery calcium score.

Most of the men participating in the Cardiovascular Trial had a severe amount of coronary atherosclerosis at baseline: 70 of 138 men (50.7%) had a coronary artery calcification score higher than 300 Agatston units. Although men in the placebo group at baseline had a somewhat greater mean coronary artery calcium score, as well as a somewhat greater mean noncalcified plaque volume by CCTA, than men in the testosterone group, these differences did not affect the comparison of changes from baseline to month 12; analyses of associations

Table 1. Baseline Characteristics of Men in the Cardiovascular Trial

Characteristic	Treatment Group	
	Testosterone (n = 73)	Placebo (n = 65)
<b>Demographics</b>		
Age <sup>a</sup>		
Mean (SD), y	70.5 (5.7)	72.0 (5.7)
No. (%)		
≤75 y	63 (86.3)	51 (78.5)
>75 y	10 (13.7)	14 (21.5)
Race, No. (%)		
White	60 (82.2)	52 (80.0)
Black	7 (9.6)	8 (12.3)
Other <sup>b</sup>	6 (8.2)	5 (7.7)
Ethnicity, No. (%)		
Hispanic	5 (6.8)	2 (3.1)
Non-Hispanic	68 (93.2)	63 (96.9)
College graduate, No. (%)	41 (56.2)	36 (55.4)
Married or living with partner, No. (%)	48 (65.8)	48 (73.8)
Study site, No. (%) <sup>a</sup>		
Albert Einstein College of Medicine	5 (6.8)	8 (12.3)
Baylor College of Medicine	9 (12.3)	9 (13.8)
Boston University Medical Center	1 (1.4)	0
Northwestern University	6 (8.2)	10 (15.4)
Harbor-UCLA Medical Center	21 (28.8)	16 (24.6)
University of Florida	4 (5.5)	5 (7.7)
University of Pittsburgh	8 (11.0)	6 (9.2)
VA Puget Sound Health Care System	7 (9.6)	2 (3.1)
Yale School of Medicine	12 (16.4)	9 (13.8)
Main trial participation, No. (%) <sup>a</sup>		
Sexual Function Trial	49 (67.1)	39 (60.0)
Physical Function Trial	34 (46.6)	35 (53.8)
Vitality Trial	51 (69.9)	40 (61.5)
<b>Concomitant conditions</b>		
BMI		
Mean (SD)	30.6 (3.8)	30.4 (3.5)
>30, No. (%)	45 (61.6)	37 (56.9)
Alcohol use, No. of drinks/wk, median (IQR)	0 (0-2)	1.0 (0-2)
Smoking, No. (%)		
Current smoker	4 (5.5)	10 (15.4)
Ever smoker	48 (65.8)	43 (66.2)
Diabetes, No. (%)	23 (31.5)	19 (29.2)
Hypertension, No. (%)	49 (67.1)	42 (64.6)
High cholesterol, No. (%)	46 (63.0)	42 (64.6)
History of myocardial infarction, No. (%)	6 (8.2)	6 (9.2)
History of stroke, No. (%)	0	2 (3.1)
Sleep apnea, No. (%)	14 (19.2)	12 (18.5)
Coronary artery revascularization, No. (%)	4 (5.5)	6 (9.2)
ACC/AHA risk score, mean (SD), % <sup>c</sup>	24 (10.9)	27 (10.5)
Coronary artery calcium score in Agatston units, No. (%) <sup>d</sup>		
0	7 (9.6)	3 (4.8)
>0 to <300	34 (46.6)	22 (34.9)
≥300	32 (43.8)	38 (60.3)

(continued)

Table 1. Baseline Characteristics of Men in the Cardiovascular Trial (continued)

Characteristic	Treatment Group	
	Testosterone (n = 73)	Placebo (n = 65)
<b>Medication use, No. (%)</b>		
Antidiabetics	20 (27.4)	18 (27.7)
Statins	45 (61.6)	40 (61.5)
Antihypertensives	46 (63.0)	39 (60.0)
Antidepressants <sup>a</sup>	8 (12.3)	12 (16.4)
PDE5 inhibitors <sup>a</sup>	3 (4.1)	4 (6.2)
<b>Sex hormones</b>		
Testosterone <sup>a</sup>		
Mean (SD), ng/dL	225.0 (56.8)	252.3 (56.4)
No. (%)		
≤200 ng/dL	23 (31.5)	12 (18.5)
>200 ng/dL	50 (68.5)	53 (81.5)
Free testosterone, mean (SD), pg/mL	59.1 (18.2)	67.6 (22.9)
Dihydrotestosterone, mean (SD), ng/dL	22.7 (16.0)	21.6 (10.0)
Estradiol, mean (SD), pg/mL	19.7 (5.2)	21.2 (6.2)
Sex hormone-binding globulin, mean (SD), μg/mL	3.4 (1.7)	3.3 (1.5)

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; PDE5, phosphodiesterase type 5.

SI conversion factors: To convert testosterone to nanomoles per liter, multiply by 0.0347; estradiol to picomoles per liter, multiply by 3.671; and sex hormone-binding globulin to nanomoles per liter, multiply by 8.896.

<sup>a</sup> Factor used to balance the treatment assignment using the minimization procedure.

<sup>b</sup> Includes Asian, North American Indian/Alaska Native, multiracial, and other.

<sup>c</sup> The 10-year risk of heart disease or stroke by the ACC/AHA risk calculator (<http://www.cvriskcalculator.com>).<sup>24</sup>

<sup>d</sup> Higher scores indicate more coronary artery calcium.

between testosterone and coronary artery calcium score were adjusted for baseline values, and results of men with baseline values higher than the median did not differ appreciably from those with baseline values below the median.

Few prior studies have examined the effect of testosterone on atherosclerosis in men. In a placebo-controlled trial in middle-aged and older men, testosterone treatment for 3 years did not affect the change from baseline in coronary artery calcium score or common carotid artery intima-media thickness.<sup>25</sup> In the Cardiovascular Trial, testosterone treatment, although for 1 year only, was not associated with a change in the coronary artery calcium score.

Coronary computed tomographic angiography, as used in the present trial, has the advantage over the coronary artery calcium score of being able to detect noncalcified coronary artery plaque and its components as well as calcified plaque. Although a relatively new technique, it appears to give similar quantitative results to intravascular ultrasonography,<sup>26,27</sup> and its excellent intraobserver and interobserver reproducibility for noncalcified plaque volume<sup>28,29</sup> makes it feasible for longitudinal studies. Noncalcified plaque volume, as determined by CCTA, has been associated with myocardial ischemia<sup>30</sup> and subsequent cardiovascular adverse events.<sup>31</sup>

Table 2. Change From Baseline and Estimated Differences for Primary, Secondary, and Exploratory Outcomes in the Cardiovascular Trial

Outcome	Treatment Group		Estimated Difference (95% CI) <sup>a</sup>	P Value <sup>b</sup>
	Testosterone (n = 73)	Placebo (n = 65)		
<b>Primary</b>				
Noncalcified plaque volume, mm <sup>3</sup>				
Baseline, median (IQR)	204 (60 to 420)	317 (168 to 589)		
Month 12, median (IQR)	232 (103 to 473)	325 (172 to 560)		
Change from baseline value, unadjusted mean (95% CI)	40 (23 to 56)	4 (-14 to 22)		
LS mean (95% CI) <sup>c</sup>	54 (12 to 97)	14 (-29 to 56)	41 (14 to 67)	.003
<b>Secondary</b>				
Total plaque volume, mm <sup>3</sup>				
Baseline, median (IQR)	272 (84 to 600)	499 (246 to 925)		
Month 12, median (IQR)	318 (133 to 693)	541 (248 to 950)		
Change from baseline value, unadjusted mean (95% CI)	57 (35 to 78)	21 (0 to 42)		
LS mean (95% CI) <sup>c</sup>	75 (22 to 128)	28 (-24 to 81)	47 (13 to 80)	.006
Coronary artery calcium score, Agatston units <sup>d</sup>				
Baseline, median (IQR)	255 (43 to 963)	494 (146 to 1892)		
Month 12, median (IQR)	244 (52 to 1013)	503 (146 to 2108)		
Change from baseline value, unadjusted mean (95% CI)	53 (25 to 82)	118 (73 to 164)		
LS mean (95% CI) <sup>c</sup>	64 (-19 to 146)	91 (7 to 174)	-27 (-80 to 26)	.31
<b>Exploratory</b>				
Low-attenuation plaque volume, mm <sup>3</sup>				
Baseline, median (IQR)	7.1 (1.5 to 32.4)	15.3 (2.6 to 31.1)		
Month 12, median (IQR)	9.5 (2.1 to 24.2)	11.0 (3.2 to 30.8)		
Change from baseline value, unadjusted mean (95% CI)	6 (0 to 12)	2 (-2 to 6)		
LS mean (95% CI) <sup>c</sup>	8 (-4 to 20)	3 (-9 to 14)	5 (-2 to 13)	.14
Fibrous-fatty plaque volume, mm <sup>3</sup>				
Baseline, median (IQR)	40.0 (11.5 to 72.6)	43.7 (18.9 to 107)		
Month 12, median (IQR)	46.3 (14.0 to 100)	54.5 (14.7 to 107)		
Change from baseline value, unadjusted mean (95% CI)	9 (1 to 17)	1 (-6 to 9)		
LS mean (95% CI) <sup>c</sup>	12 (-7 to 30)	2 (-17 to 21)	10 (-2 to 21)	.11
Fibrous plaque volume, mm <sup>3</sup>				
Baseline, median (IQR)	160 (51.5 to 305)	254 (122 to 426)		
Month 12, median (IQR)	177 (64.1 to 320)	253 (138 to 471)		
Change from baseline value, unadjusted mean (95% CI)	25 (14 to 35)	1 (-13 to 15)		
LS mean (95% CI) <sup>c</sup>	31 (0 to 62)	7 (-24 to 37)	24 (5 to 43)	.01
Dense calcium plaque volume, mm <sup>3</sup>				
Baseline, median (IQR)	69.5 (13.6 to 211)	173 (35.2 to 351)		
Month 12, median (IQR)	74.8 (13.9 to 245)	177 (47.2 to 323)		
Change from baseline value, unadjusted mean (95% CI)	17 (7 to 27)	17 (6 to 28)		
LS mean (95% CI) <sup>c</sup>	17 (-8 to 42)	11 (-14 to 36)	5 (-11 to 21)	.51

Abbreviations: IQR, interquartile range; LS, least squares.

<sup>a</sup> Mean difference in change from baseline for participants assigned to testosterone vs those assigned to placebo, with adjustment for balancing factors: baseline total testosterone level ( $\leq 200$  or  $>200$  ng/dL [to convert to nanomoles per liter, multiply by 0.0347]), age ( $\leq 75$  or  $>75$  years), trial site, participation in the main trials, use or nonuse of antidepressants, use or nonuse of phosphodiesterase type 5 inhibitors, and baseline value of the outcome variable.

<sup>b</sup> Determined by a linear mixed model with all balancing factors and baseline outcome value as covariates and a random effect for participant.

<sup>c</sup> Adjusted treatment group mean of the change from baseline to month 12.

<sup>d</sup> Higher values indicate more coronary artery calcium.

The increase in coronary artery noncalcified and total plaque volumes in men treated with testosterone is concerning because any limitation of the vascular lumen could be considered deleterious.<sup>32</sup> The clinical significance of these increases could depend on the differential effects of testosterone on the individual components of noncalcified plaque. Testosterone treatment was associated with a significant increase in the volume of fibrous plaque, which may be more stable than other types of plaque.<sup>33</sup> A recent review, however,

concluded that total plaque burden may be more important than the radiologic characteristics of individual plaques.<sup>32</sup>

This trial had several strengths, including a placebo-controlled design, selection of men with unequivocally low testosterone, and a relatively high retention rate. This study also has limitations. One limitation is that the results apply only to men aged 65 years or older who have low testosterone. Another limitation is that the assumptions about the composition of plaque components as detected by CCTA



have not been confirmed by direct radiologic-pathologic studies. Furthermore, the volume and radiologic characteristics of coronary artery plaques are only surrogate outcomes and do not account for other factors that can influence the frequency and extent of plaque rupture and thrombosis. The major limitation is that the trial was not large enough or long enough to draw conclusions about the risk of testosterone treatment on major adverse cardiovascular events.

## Conclusions

Among older men with symptomatic hypogonadism, treatment with testosterone gel for 1 year compared with placebo was associated with a significantly greater increase in coronary artery noncalcified plaque volume, as measured by CCTA. Larger studies are needed to understand the clinical implications of this finding.

### ARTICLE INFORMATION

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boards for AbbVie, Apricus, Clarus Therapeutics, Endo Pharma, Ferring, Lilly, Pfizer, and Repros Therapeutics. Dr A. M. Matsumoto reported receiving research support from AbbVie; receiving consulting fees from AbbVie, Endo, Lilly, the US Anti-Doping Agency, and Lipocine; receiving personal fees from Clarus Therapeutics; receiving royalties from UpToDate; and serving on the scientific advisory board for the Partnership for Clean Competition. Dr Molitch reported serving as a consultant to AbbVie (Abbott Laboratories), Eli Lilly & Co, and Pfizer. Dr Basaria reported serving as a consultant to Eli Lilly and Takeda Pharmaceuticals. Dr Wang reported receiving research support from Clarus Therapeutics, Lipocine, Antares, and Besins; and serving on advisory committees for Lipocine, Antares, TesoRX, and Besins. Dr Snyder reported serving as a consultant to Watson Laboratories. No other disclosures were reported.

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