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Effect of Testosterone on Cardiovascular Biomarkers

THE EFFECT OF TESTOSTERONE ON CARDIOVASCULAR BIOMARKERS IN THE TESTOSTERONE TRIALS

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Context: Studies of the possible cardiovascular risk of testosterone treatment are inconclusive.

Objective: To determine the effect of testosterone treatment on cardiovascular (CV) biomarkers in older men with low testosterone.

Design: Double-blind, placebo-controlled trial

Setting: Twelve academic medical centers in the United States

Participants: 788 men ≥ 65 years old with an average of two serum testosterone levels < 275 ng/dL who were enrolled in The Testosterone Trials.

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

Main Outcome Measures: Serum markers of cardiovascular risk, including lipids and markers of glucose metabolism, fibrinolysis, inflammation, and myocardial damage.

Results: Testosterone treatment, compared to placebo, significantly decreased total cholesterol (adjusted mean difference -6.1 mg/dL, $p < 0.001$), high density lipoprotein (HDL) cholesterol (adjusted mean difference -2.0 mg/dL, $p < 0.001$) cholesterol and low density lipoprotein (LDL) cholesterol (adjusted mean difference -2.3 mg/dL, $p = 0.051$) from baseline to month 12.

Testosterone also slightly but significantly decreased fasting insulin (adjusted mean difference -1.7 μ IU/mL, $p = 0.02$) and HOMA-IR (adjusted mean difference -0.6 , $p = 0.03$). Testosterone did not change triglycerides, D-dimer, C-reactive protein, interleukin-6, troponin, glucose or HgbA1c more than placebo.

Conclusions and Relevance: Testosterone treatment for one year of older men with low testosterone was associated with small reductions in cholesterol and insulin but not with other glucose markers or markers of inflammation or fibrinolysis or with troponin. The clinical importance of these findings is unclear and requires a larger trial of clinical outcomes.

Testosterone treatment, compared to placebo, of older men with low testosterone was associated with small reductions in total, HDL and LDL cholesterol and in insulin and HOMA-IR but not glucose.

INTRODUCTION

The effect of testosterone treatment on cardiovascular risk is uncertain. Some retrospective studies using electronic medical records have reported more cardiovascular adverse events in men taking testosterone than in men not taking it, but others have not¹⁻⁴. These studies all have the limitations of not being controlled for diagnosis or treatment. One clinical trial of testosterone in frail older men was stopped early because more cardiovascular adverse events occurred in men taking testosterone than in men taking placebo⁵, but another similar trial reported few adverse cardiovascular events⁶. Meta-analyses of clinical trials have generally not shown more adverse cardiovascular events in men taking testosterone than in men taking placebo, but none of the individual trials was designed prospectively to capture these events^{7,8}.

The Testosterone Trials (TTrials) were a group of seven coordinated trial in 788 men to determine the efficacy of raising the serum testosterone levels of men ≥ 65 years to normal for young men for one year⁹. Although the numbers of men who experienced major adverse cardiovascular events were similar in the two treatment arms in all men in the TTrials¹⁰, testosterone treatment was associated with a greater increase in noncalcified coronary artery plaque volume by computed tomographic angiography in the 138 men who participated in the Cardiovascular Trial¹¹.

If testosterone does affect cardiovascular risk, it might do so by altering any one of several cardiovascular risk factors, such as lipids, glucose metabolism, coagulation and inflammation. We therefore measured several biomarkers of cardiovascular risk at baseline and after 3 and 12 months of treatment in all men participating in the TTriaals.

METHODS

Study Design

The TTriaals were a coordinated group of seven double-blind, placebo-controlled trials designed to evaluate the efficacy of testosterone treatment in men ≥ 65 years who had age-related low testosterone levels⁹. To participate in the TTriaals, a man had to qualify for at least one of the three main trials (Sexual Function, Physical Function and Vitality). Those who qualified could also participate in any of the other trials if they met the respective entry criteria. The participants were allocated to receive testosterone or placebo gel for one year. This report describes the serum levels of cardiovascular biomarkers at baseline and months 3 and 12 in all men participating in the TTriaals.

The institutional review boards of the 12 participating sites approved the TTriaals protocols. Before trial-related procedures were conducted, all participants provided written informed consent. An independent Data and Safety Monitoring Board oversaw participant safety and trial conduct.

Participants

The inclusion and exclusion criteria have been published⁹. In brief, men were included who were ≥ 65 years, had serum testosterone levels that averaged < 275 ng/dL on two morning samples and had a subjective and objective evidence of sexual dysfunction, physical dysfunction and/or reduced vitality. Men were excluded who were at moderate or high risk for prostate cancer, had a myocardial infarction within the previous three months, or had a blood pressure > 160 mm Hg systolic or 100 mm Hg diastolic, serum creatinine > 2.2 mg/dL or hemoglobin A1c $> 8.5\%$. Men who were taking medications to control blood pressure or serum lipids were not excluded.

Testosterone Treatment

Men were allocated to receive either testosterone as a 1% gel in a pump bottle (AndroGel, AbbVie) or similar placebo gel in a double-blind fashion for one year. The initial dose of testosterone was 5g a day. The dose was adjusted to keep the serum concentration within the normal range for young men on the basis of measurement in a central laboratory (Quest Clinical Trials, Valencia, CA) at months 1, 2, 3, 6 and 9. To maintain the blind, when the dose was changed in a man taking testosterone, the dose was also changed in a man taking placebo.

Assessments

Blood for cardiovascular biomarkers was drawn fasting in the morning at baseline and months 3 and 12; serum was stored at -80°C . Biomarker assays were performed at the Laboratory for Clinical Biochemistry Research, University of Vermont, with the exception of the troponin I assay, which was performed at the University of Minnesota. Samples from the same participant were assayed in the same batch. Clinical variables were measured at baseline and months 3, 6, 9 and 12.

Lipid Assays

Lipid assays included total cholesterol (interassay CV range 1.45-2.33%), high density lipoprotein (HDL) cholesterol (interassay CV range 1.69-2.26%), and triglycerides (interassay

CV range 1.95-2.57%) using enzymatic colorimetric assays (Cobas Integra 400, Roche Diagnostics, Indianapolis, IN). Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula when the triglyceride concentration was <400 mg/dL.

Glucose, Insulin and Hemoglobin A1c Assays

Glucose concentration was determined using a hexokinase method (Cobas Integra 400, Roche Diagnostics, Indianapolis, IN) (interassay CV range 2.24-4.55%).

Insulin was measured by electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics, Indianapolis, IN) (interassay CV range 2.39-2.78%).

HbA1c was measured in frozen whole blood samples by turbidmetric inhibition immunoassay (Tina-quant HgA1C Gen 2 Whole Blood application, Cobas Integra 400, Roche Diagnostics, Indianapolis, IN) (interassay CV range 1.63-3.25%).

Assays of Markers of Inflammation

C-reactive protein (CRP) was measured using a high-sensitivity particle enhanced immunonephelometric assay (BNII nephelometer; Siemens, Inc., Deerfield, IL) (interassay CV range 3.32-4.64%). Interleukin-6 (IL-6) was measured by electrochemiluminescence immunoassay (Meso Scale Diagnostics, Rockville, MD) (interassay CV range 8.14-11.95%).

D-Dimer and Troponin Assays

D-dimer was measured using an immunoturbidimetric assay (STA-R Evolution, Diagnostica Stago, Parsippany, NJ) (interassay CV range 2.73-20.14%).

Troponin I was measured using a high-sensitivity immunoassay (ARCHITECT STAT high-sensitive troponin I assay; Abbott Laboratories, Abbott Park, IL).

Statistical analyses

The effects of testosterone were assessed using random effects models for longitudinal data. The models included visit time as a categorical variable and a single main effect for treatment, and adjusted for baseline values of each biomarker and all balancing variables used in the allocation procedure: study site, indicator variables of participation in each primary efficacy trial, baseline testosterone concentration (\leq or >200 ng/dL), age (\leq or >75), use of anti-depressants, and use of PDE-5 inhibitors. All participants who had at least one post-baseline value were included in the intent-to-treat analysis. We performed additional analyses of lipid markers excluding men who were not taking lipid-lowering medications at baseline but initiated them during the study; we also performed separate analyses of metabolic markers excluding men taking antidiabetic medications. Significance was assessed through the two-sided Wald test and confidence interval for the treatment effect. The treatment effect denotes the average difference in response by treatment arm across all visits (baseline, months 3 and 12). No adjustments were made for multiple testing.

RESULTS

Participants and Clinical Measures

Trial enrollment was 788 men at 12 sites. The mean age at baseline was 72 years. Relatively high percentages were obese and had co-morbid conditions, such as diabetes and hypertension, but the two treatment arms were well balanced for these conditions and related medications (Table 1). Testosterone treatment increased the serum testosterone concentration from unequivocally low at baseline to mid-normal for young men by month 3 and maintained it at that level through month 12¹⁰. Testosterone treatment, compared to placebo, did not significantly

change weight (adjusted difference 0.28 kg, $p = 0.18$), BMI (adjusted difference 0.09 kg/m², $p = 0.21$) or waist/hip ratio (adjusted difference 0.002, $p = 0.46$) (Table 2).

Lipids

Serum concentrations of lipids (Table 3) were evaluated for all men and then separately for men who were either consistently taking or not taking lipid-lowering drugs during the 12 months of treatment. Levels at baseline were slightly lower in men in the testosterone arm (total cholesterol 161.9 mg/dL; HDL cholesterol, 44.5 mg/dL; LDL cholesterol, 87.9 mg/dL) than in men in the placebo arm (total cholesterol 167.8 mg/dL; HDL, 45.5 mg/dL; LDL, 91.8 mg/dL). Lipid levels decreased during the 12 months of treatment in both treatment arms. Adjusting for baseline levels and balancing factors, the men treated with testosterone had a reduction in total cholesterol 6.1 mg/dL greater than men treated with placebo ($p < 0.001$). Reductions in HDL cholesterol (adjusted difference -2.0 mg/dL, $p < 0.001$) and in non-HDL cholesterol (adjusted difference -4.2, $p = 0.005$) were also greater in men treated with testosterone than men treated with placebo. Change in LDL cholesterol was marginally greater in the testosterone arm; the adjusted difference in change was 2.3 mg/dL, $p = 0.051$). Reductions in triglyceride values were not significantly associated with treatment assignment.

Eleven men in the testosterone arm and four in the placebo arm initiated lipid-lowering medication after baseline. To assess the impact of these medication changes, we performed an analysis excluding these 15 men; the results changed minimally.

Markers of Glucose Metabolism

We evaluated markers that reflect glucose metabolism (Table 4) in all men and separately in men who were not taking medications for diabetes during the trial. Mean levels were similar in the 2 treatment groups at baseline (fasting glucose, 114.4 mg/dL vs 116.0 mg/dL; fasting insulin, 18.6 μ U/mL vs 18.1 μ U/mL; Homeostatic Model Assessment-Insulin Resistance (HOMA-IR), 5.8 vs 5.9; HgbA1c, 6.3% vs 6.3%, in the testosterone and placebo arms, respectively). Changes from baseline in these markers were small in both groups, but some differences in the changes between treatment arms were statistically significant (glucose, 1.3 mg/dL vs 2.2 mg/dL, adjusted difference -1.5 mg/dL, $p = 0.30$; insulin, -1.8 μ U/mL vs -0.7 μ U/mL, adjusted difference -1.7 μ U/mL, $p = 0.02$; HOMA-IR, 0.3 vs -0.2, adjusted difference -0.6, $p = 0.03$; HgbA1c, 0.0% vs 0.1%, adjusted difference -0.07%, $p = 0.09$, for men in the testosterone group vs placebo group, respectively). Evaluation of these markers in men not taking antidiabetic medications showed no statistically significant effect of testosterone.

Other Markers

We also measured D-dimer as a marker of fibinolysis, C-reactive protein (CRP) and interleukin-6 (IL-6) as markers of inflammation, and troponin as a marker of myocardial damage (Table 5). All showed similar mean baseline values (D-dimer, 0.7 mg/L vs 0.7 mg/L; CRP, 3.5 mg/L vs 3.5 mg/L; IL-6, 1.9 pg/mL vs 2.0 pg/mL; troponin, 7.6 ng/L vs 9.1 ng/L, in the testosterone and placebo groups, respectively). Mean changes from baseline were small and similar between treatment groups (D-dimer, 0.1 mg/L vs 0.1 mg/L, adjusted difference 0.01, $p = 0.69$; CRP, -0.7 mg/L vs -0.1 mg/L, adjusted difference -0.6 mg/L, $p = 0.11$; IL-6, 0.9 pg/ml vs 0.2 pg/mL, adjusted difference 0.2 pg/mL, $p = 0.67$; troponin, 2.4 ng/L vs 0.1 ng/mL, adjusted difference 0.9 mg/L, $p = 0.37$).

Because testosterone treatment was associated with a greater increase in coronary artery plaque volume in the 138 men who participated in the Cardiovascular Trial¹¹, we repeated all of the analyses of the effect of testosterone in just the 138 men who participated in the

Cardiovascular Trial. The results were similar in these 138 men to the results in all TTrials participants.

DISCUSSION

In The Testosterone Trials, raising the serum testosterone concentrations of men ≥ 65 years who had low baseline testosterone to normal levels for young men for one year did not affect weight, BMI or waist/hip ratio but decreased slightly serum concentrations of total, HDL and LDL cholesterol. The total cholesterol/HDL cholesterol ratio was not altered. Testosterone treatment also decreased slightly markers of insulin resistance but did not change fasting glucose or hemoglobin A1c levels. Testosterone treatment did not change appreciably markers of inflammation, fibrinolysis or myocardial damage.

Prior trials of the effects of injectable testosterone esters on serum lipids in hypogonadal men have also demonstrated small reductions in serum total, HDL and LDL cholesterol¹². Meta-analyses of testosterone trials that included variable entry criteria for participants, routes of administration and doses have shown inconsistent effects on cholesterol^{8,13}. In a double-blind crossover study of injectable testosterone versus placebo in 24 hypogonadal men with type 2 diabetes, testosterone treatment was associated with improved insulin sensitivity and glycated hemoglobin levels¹⁴, but meta-analyses have generally not reported an effect of testosterone on glucose metabolism⁸. Several studies have shown no clear effects of testosterone treatment on various inflammatory markers¹⁵⁻¹⁷.

Compared to the effect of statin drugs on lowering LDL cholesterol, the effect of testosterone in this trial is quite small. Statin drugs, in doses used clinically, lower LDL cholesterol by 10-80 mg/dL¹⁸, compared to the mean reduction of 2.3 mg/dL associated with testosterone treatment in this trial. Compared to the effect of statin drugs raising HDL cholesterol, the effect of testosterone on lowering HDL cholesterol is similar. Statin drugs, in doses used clinically, raise HDL cholesterol by 2-3 mg/dL¹⁹, similar in magnitude to the reduction of 2.0 mg/dL associated with testosterone treatment in this trial. Ingestion of 17-alkylated androgens, which are abused by athletes, decreases HDL cholesterol much more than testosterone itself.²⁰

The results presented here are important because of the many strengths of the TTrials, including the large number of participants, the placebo-controlled design, raising the median serum testosterone level from unequivocally low to mid-normal for young men, and the excellent participant retention. One limitation of this trial is that the results apply only to older men with low testosterone. Another limitation is that all of the cardiovascular markers assessed were surrogates and not clinical outcomes. Yet another limitation is that we did not assess the function of the lipoproteins, such as the effect of HDL on cholesterol transport.²¹

The clinical significance of the decreases in cholesterols is uncertain, because both LDL and HDL cholesterol fell, both to small degrees, and insulin and HOMA-IR fell but only slightly. In the 138 men in the TTrials who underwent CT angiography at baseline and month 12, testosterone treatment was associated with a greater increase in noncalcified coronary artery plaque volume than placebo treatment, yet in all TTrials participants, a similar number of men (seven) in each treatment arm experienced major adverse cardiovascular events¹⁰. A trial of a much larger number of men treated for a much longer time would be necessary to determine if testosterone treatment of hypogonadal men affects clinical cardiovascular risk.

We conclude that raising the serum testosterone levels of men ≥ 65 years with low testosterone to normal levels for young men decreases slightly their serum cholesterol and insulin levels, but the clinical significance of these small decreases is unknown.

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Table 1. Characteristics of Participants at Baseline¹.

Characteristic	Treatment	
	Testosterone	Placebo
N	394	394
Demographics		
Age (yr)	72 ± 5.7	72 ± 5.8
Height (cm)	175 ± 7.1	175 ± 7.0
Weight (kg)	95 ± 13.1	95 ± 14.0
BMI (kg/m ²)	31 ± 3.6	31 ± 3.5
BMI >30 (%)	251 (63.7%)	246 (62.4%)
Waist/Hip Ratio	1.0 ± 0.1	1.0 ± 0.1
Concomitant Conditions		
Diabetes (%)	148 (37.6%)	144 (36.5%)
Hypertension (%)	286 (72.6%)	279 (70.8%)
History of Myocardial Infarction	53 (13.5%)	63 (16.0%)
History of Stroke	16 (4.1%)	17 (4.3%)
Medications		
Antidiabetics	130 (33.0%)	131 (33.2%)
Lipid-lowering drugs	274 (69.5%)	273 (69.3%)

¹Values are mean ± SD or number (%)

Table 2. Clinical Measures¹

Measure	Testosterone					Placebo					Difference in change over time ² (95% CI)	P-value
	Baseline (n)	Month 3 (n)	Month 6 (n)	Month 9 (n)	Month 12 (n)	Baseline (n)	Month 3 (n)	Month 6 (n)	Month 9 (n)	Month 12 (n)		
Weight (kg)	94.8±13.1 (394)	95.4±12.9 (374)	94.6±13.1 (367)	94.6±12.9 (356)	94.1±13.3 (367)	94.8±14.0 (394)	94.7±14.0 (371)	94.1±14.1 (349)	93.5±14.0 (341)	93.4±14.1 (353)	0.28 (-0.13, 0.69)	0.18
BMI (kg/m²)	31.0±3.6 (394)	31.2±3.6 (374)	30.9±3.6 (367)	30.9±3.6 (356)	30.8±3.6 (367)	31.0±3.6 (394)	30.9±3.5 (371)	30.8±3.6 (349)	30.7±3.6 (341)	30.7±3.7 (353)	0.09 (-0.05, 0.24)	0.21
Waist/hip ratio	1.0±0.1 (394)	1.0±0.1 (373)	1.0±0.1 (367)	1.0±0.1 (356)	1.0±0.1 (366)	1.0±0.1 (394)	1.0±0.1 (369)	1.0±0.1 (349)	1.0±0.1 (342)	1.0±0.1 (353)	-0.002 (-0.006, 0.003)	0.46

¹ Values are means ± SD (number)

² Average over all observations, adjusting for balancing factors and baseline value. Positive values mean men in the testosterone arm increased more, or decreased less, than men in placebo arm; negative values mean men in placebo arm increased more, or decreased less, than men in testosterone arm.

Table 3. Serum Concentrations of Lipids¹

Assay	Testosterone			Placebo			Difference in change over time ²	P-value
	Baseline (n)	Month 3 (n)	Month 12 (n)	Baseline (n)	Month 3 (n)	Month 12 (n)		
Cholesterol (mg/dL)	161.9 ± 37.1 (369)	153.7 ± 35.1 (367)	154.9 ± 32.3 (346)	167.8 ± 33.8 (369)	164.5 ± 36.5 (367)	164.6 ± 34.6 (333)	-6.1 (-8.9, -3.3)	<0.001
HDL Cholesterol (mg/dL)	44.5 ± 12.7 (369)	41.8 ± 12.2 (367)	43.1 ± 12.6 (346)	45.5 ± 14.4 (369)	44.8 ± 13.3 (367)	45.3 ± 13.1 (333)	-2.0 (-2.9, -1.0)	<0.001
Non-HDL Cholesterol (mg/dL)	117.4 ± 37.2 (369)	111.9 ± 34.7 (367)	111.8 ± 31.9 (346)	122.2 ± 35.2 (369)	119.7 ± 37.1 (367)	119.3 ± 35.4 (333)	-4.2 (-7.1, -1.3)	0.005
LDL Cholesterol (mg/dL)	87.9 ± 28.9 (363)	84.0 ± 28.2 (360)	84.9 ± 27.7 (341)	91.8 ± 29.6 (360)	89.1 ± 30.5 (363)	89.7 ± 27.8 (325)	-2.3 (-4.6, 0.01)	0.051
Cholesterol/HDL Ratio	3.9 ± 2.1 (369)	4.0 ± 1.5 (367)	3.9 ± 1.6 (346)	4.0 ± 1.4 (369)	4.0 ± 1.4 (367)	3.9 ± 1.4 (333)	0.02 (-0.1, 0.2)	0.81
Triglycerides (mg/dL)	150.1 ± 149.3 (369)	145.6 ± 136.0 (367)	140.7 ± 142.6 (346)	153.4 ± 84.3 (369)	151.3 ± 81.2 (367)	145.1 ± 77.5 (333)	-4.0 (-14.7, 6.8)	0.47

¹ Values are means ± SD and (number of participants)

² Average over all observations, adjusting for balancing factors and baseline value. Positive values mean men in the testosterone arm increased more, or decreased less, than men in placebo arm; negative values mean men in placebo arm increased more, or decreased less, than men in testosterone arm.

Table 4. Markers of Glucose Metabolism¹

Assay	Testosterone			Placebo			Difference in change over time ² (95% CI)	P-value
	Baseline (n)	Month 3 (n)	Month 12 (n)	Baseline (n)	Month 3 (n)	Month 12 (n)		
Glucose (mg/dL)	114.4 ± 28.2 (369)	113.6 ± 32.4 (367)	115.7 ± 30.9 (346)	116.0 ± 27.8 (369)	116.1 ± 29.1 (367)	118.2 ± 35.2 (333)	-1.5 (-4.3, 1.3)	0.30
Insulin (μU/mL)	19.6 ± 19.0 (367)	17.3 ± 12.5 (365)	17.9 ± 13.6 (342)	17.5 ± 12.2 (364)	19.2 ± 14.8 (365)	19.3 ± 14.9 (330)	-1.7 (-3.1, -0.3)	0.02
HOMA-IR³	5.8 ± 6.3 (367)	5.1 ± 4.6 (365)	5.5 ± 6.4 (342)	5.8 ± 6.0 (364)	5.9 ± 6.2 (365)	5.6 ± 5.5 (330)	-0.6 (-1.2, -0.1)	0.03
Hgb A1C⁴ (%)	6.3 ± 0.8 (249)	---	6.3 ± 0.9 (250)	6.3 ± 0.8 (243)	---	6.4 ± 1.0 (242)	-0.07 (-0.2, 0.01)	0.09

¹ Values are means ± SD and (number of participants)

² Average over all observations, adjusting for balancing factors and baseline value. Positive values mean men in the testosterone arm increased more, or decreased less, than men in placebo arm; negative values mean men in placebo arm increased more, or decreased less, than men in testosterone arm.

³ HOMA-IR. Homeostatic model assessment of insulin resistance, calculated as glucose x insulin /22.5.

⁴Hgb A1c. Hemoglobin A1c. Collection of blood for hgb A1c was not begun until after the trial was underway, so the n is smaller for this parameter.

Table 5. Other Markers¹

Assay	Testosterone			Placebo			Difference in change over time ² (95% CI)	P-value
	Baseline (n)	Month 3 (n)	Month 12 (n)	Baseline (n)	Month 3 (n)	Month 12 (n)		
D-dimer (mg/L)	0.7 ± 0.6 (370)	0.8 ± 1.2 (367)	0.8 ± 0.6 (351)	0.7 ± 0.6 (367)	0.8 ± 0.7 (364)	0.8 ± 0.8 (333)	0.01 (-0.1 – 0.1)	0.69
CRP³ (mg/L)	3.5 ± 9.4 (363)	3.4 ± 6.2 (363)	2.8 ± 3.8 (347)	3.5 ± 5.6 (363)	3.9 ± 9.1 (362)	3.4 ± 7.4 (332)	-0.60 (-1.3 – 0.1)	0.11
IL-6⁴ (pg/mL)	1.9 ± 5.8 (372)	2.0 ± 1.9 (371)	2.8 ± 18.3 (352)	2.0 ± 2.4 (371)	2.2 ± 2.9 (367)	2.2 ± 3.0 (336)	0.2 (-0.6 – 0.9)	0.67
Troponin (ng/mL)	7.6 ± 7.4 (317)	9.1 ± 9.7 (316)	10.0 ± 15.0 (262)	9.1 ± 18.3 (307)	9.4 ± 17.4 (327)	9.2 ± 19.1 (278)	0.9 (-1.1 – 2.9)	0.37

1. Values are means ± SD and (number of participants)
2. Average over all observations, adjusting for balancing factors and baseline value. Positive values mean men on testosterone arm increased more, or decreased less, than men on placebo arm; negative values mean men in placebo arm increased more, or decreased less, than men on testosterone arm.
3. CRP. C-reactive protein
4. IL-6. Interleukin 6.

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