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Effects of Testosterone Treatment in Older Men

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Abstract

BACKGROUND—Serum testosterone concentrations decrease as men age, but benefits of raising testosterone levels in older men have not been established.

METHODS—We assigned 790 men 65 years of age or older with a serum testosterone concentration of less than 275 ng per deciliter and symptoms suggesting hypoandrogenism to receive either testosterone gel or placebo gel for 1 year. Each man participated in one or more of three trials — the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial. The primary outcome of each of the individual trials was also evaluated in all participants.

RESULTS—Testosterone treatment increased serum testosterone levels to the mid-normal range for men 19 to 40 years of age. The increase in testosterone levels was associated with significantly increased sexual activity, as assessed by the Psychosexual Daily Questionnaire ($P<0.001$), as well as significantly increased sexual desire and erectile function. The percentage of men who had an increase of at least 50 m in the 6-minute walking distance did not differ significantly between the two study groups in the Physical Function Trial but did differ significantly when men in all three trials were included (20.5% of men who received testosterone vs. 12.6% of men who received placebo, $P=0.003$). Testosterone had no significant benefit with respect to vitality, as assessed by the Functional Assessment of Chronic Illness Therapy–Fatigue scale, but men who received testosterone reported slightly better mood and lower severity of depressive symptoms than those who received placebo. The rates of adverse events were similar in the two groups.

CONCLUSIONS—In symptomatic men 65 years of age or older, raising testosterone concentrations for 1 year from moderately low to the mid-normal range for men 19 to 40 years of age had a moderate benefit with respect to sexual function and some benefit with respect to mood and depressive symptoms but no benefit with respect to vitality or walking distance. The number of participants was too few to draw conclusions about the risks of testosterone treatment. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00799617.)

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*A complete list of investigators in the Testosterone Trials is provided in the Supplementary Appendix, available at NEJM.org.

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The authors' full names, academic degrees, and affiliations are listed in the Appendix.

Testosterone concentrations in men decrease with increasing age.[1,2] Many symptoms and conditions similar to those that are caused by low testosterone levels in men with pituitary or testicular disease become more common with increasing age. Such symptoms include decreases in mobility, sexual function, and energy. These parallels suggest that the lower testosterone levels in older men may contribute to these conditions.

Previous trials of testosterone treatment in men 65 years of age or older, however, have yielded equivocal results. Although testosterone treatment consistently increased muscle mass and decreased fat mass,[3,4] effects on physical performance,[3,5,6] sexual function,[3,6,7] and energy[3,6,8] have been inconsistent.

In 2003, an Institute of Medicine panel concluded that there was insufficient evidence that testosterone treatment was beneficial in older men[9] and recommended a coordinated set of clinical trials to determine whether testosterone would benefit older men who had low testosterone levels for no known reason other than age and who had clinical conditions to which low testosterone might contribute. The Testosterone Trials were designed to implement that recommendation.[10]

METHODS

STUDY DESIGN AND OVERSIGHT

The Testosterone Trials are a coordinated set of seven double-blind, placebo-controlled trials that are being conducted at 12 sites.[10] To enroll in these trials overall, participants had to qualify for at least one of the three main trials (the Sexual Function Trial, the Physical Function Trial, or the Vitality Trial), but they could participate in more than one if they qualified. Participants were assigned to receive testosterone gel or placebo gel for 1 year. Efficacy was assessed at baseline and at 3, 6, 9, and 12 months. Data on adverse events were collected during the treatment period and for 12 months afterward. This report describes the efficacy results for the three main trials and adverse events in all the participants in these trials.

The protocol and consent forms were approved by the institutional review boards at the University of Pennsylvania and each participating trial site. All participants provided written informed consent. A data and safety monitoring board monitored data in an unblinded fashion every 3 months. The protocol, consent forms, and statistical analysis plan are available with the full text of this article at NEJM.org.

The investigators developed the protocol with assistance from the National Institutes of Health. AbbVie, one of the funders of the trial, donated the testosterone and placebo gels but did not participate in the design or conduct of the trials or in the analysis, review, or reporting of the data before the manuscript was submitted for publication. All the authors participated in the design and conduct of the trials. Trial statisticians performed all data analyses. The first author wrote the first draft of the manuscript, and all the authors contributed to subsequent drafts.

PARTICIPANTS

Participants were recruited principally through mass mailings.[11] Respondents were screened first by telephone interview and then during two clinic visits. Eligibility criteria included an age of 65 years or older and serum testosterone levels that averaged less than 275 ng per deciliter. Exclusion criteria were a history of prostate cancer, a risk of all prostate cancer of more than 35% or of high-grade prostate cancer of more than 7% as determined according to the Prostate Cancer Risk Calculator,[12] an International Prostate Symptom Score (IPSS; range, 0 to 35, with higher scores indicating more severe symptoms of benign prostatic hyperplasia) of more than 19, conditions known to cause hypogonadism, receipt of medications that alter the testosterone concentration, high cardiovascular risk (myocardial infarction or stroke within the previous 3 months, unstable angina, New York Heart Association class III or IV congestive heart failure, a systolic blood pressure >160 mm Hg, or a diastolic blood pressure >100 mm Hg), severe depression (defined by a score of ≥20 on the Patient Health Questionnaire 9 [PHQ-9; range, 0 to 27, with higher scores indicating greater severity of depressive symptoms]), and conditions that would affect the interpretation of the results.

Inclusion in the Sexual Function Trial required self-reported decreased libido, a score of 20 or less on the sexual-desire domain (range, 0 to 33, with higher scores indicating greater desire) of the Derogatis Interview for Sexual Functioning in Men–II (DISF-M-II),[13] and a partner willing to have intercourse twice a month. Inclusion in the Physical Function Trial required self-reported difficulty walking or climbing stairs and a gait speed of less than 1.2 m per second on the 6-minute walk test.[14] Men who were not ambulatory or who had disabling neuromuscular or arthritic conditions were excluded. Inclusion in the Vitality Trial required self-reported low vitality and a score of less than 40 on the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale (range, 0 to 52, with higher scores indicating less fatigue).[15]

STUDY TREATMENT

We assigned participants to testosterone or placebo by means of a minimization technique, with participants assigned to the study treatment that best balanced the balancing factors between groups with 80% probability.[16,17] Balancing variables included participation in the main trials, trial site, screening testosterone concentration (≤200 or >200 ng per deciliter), age (≤75 or >75 years), use or nonuse of antidepressants, and use or nonuse of phosphodiesterase type 5 inhibitors.

The testosterone preparation was AndroGel 1% in a pump bottle (AbbVie). The initial dose was 5 g daily. The placebo gel was formulated to have a similar application and appearance. Serum testosterone concentration was measured at months 1, 2, 3, 6, and 9 in a central laboratory (Quest Clinical Trials), and the dose of testosterone gel was adjusted after each measurement in an attempt to keep the concentration within the normal range for young men (19 to 40 years of age). To maintain blinding when the dose was adjusted in a participant receiving testosterone, the dose was changed simultaneously in a participant receiving placebo.

ASSESSMENTS

At the end of the trials, the serum concentrations of total testosterone, free testosterone, dihydrotestosterone, estradiol, and sex hormone–binding globulin were measured in serum samples frozen at −80°C (see the Supplementary Appendix, available at NEJM.org). Steroid assays were performed at the Brigham Research Assay Core Laboratory (Boston) by liquid chromatography with tandem mass spectroscopy, and free testosterone was measured by equilibrium dialysis. All samples from each participant were measured in the same assay run.

Serum prostate-specific antigen (PSA) was measured and a digital rectal examination was performed at months 3 and 12, and PSA was measured at month 18. Detection of a prostate nodule or a confirmed increase in the PSA level by at least 1.0 ng per milliliter above baseline led to referral to the site urologist for consideration of prostate biopsy. The IPSS was determined at months 3 and 12. At every visit, adverse events were recorded and a cardiovascular-event questionnaire (see the protocol) was administered. Cardiovascular events were adjudicated by two cardiologists and two neurologists (see the Supplementary Appendix).

OUTCOMES

Efficacy outcomes were assessed at baseline and after 3, 6, 9, and 12 months of treatment. Dichotomous outcomes were used when a clinically important difference had previously been established. The primary efficacy outcome of each trial and the secondary outcomes of the Physical Function Trial were assessed in all participants; secondary outcomes for the other trials were assessed only in participants in those trials.

The primary outcome of the Sexual Function Trial was the change from baseline in the score for sexual activity (question 4) on the Psycho-sexual Daily Questionnaire (PDQ-Q4; range, 0 to 12, with higher scores indicating a greater number of activities).[10,18] Secondary outcomes were changes in the score on the erectile-function domain (range, 0 to 30, with higher scores indicating better function) of the International Index of Erectile Function (IIEF)[19] and the sexual-desire domain of the DISF-M-II.[13] Details on the assessments in the Sexual Function Trial are provided in the protocol. The primary outcome of the Physical Function Trial was the percentage of men who increased the distance walked in the 6-minute walk test by at least 50 m.[10,14] Secondary outcomes were the percentage of men whose score on the physical-function domain (PF-10; range, 0 to 100, with higher scores indicating better function) of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) increased by at least 8 points[20] and changes from baseline in the 6-minute walking distance and PF-10 score. The primary outcome of the Vitality Trial was the percentage of men whose score on the FACIT–Fatigue scale increased by at least 4 points[10,15]; secondary outcomes were the change from baseline in the FACIT–Fatigue, the score on the vitality scale (range, 0 to 100, with higher scores indicating more vitality) of the SF-36,[21] scores on the Positive and Negative Affect Schedule (PANAS) scales (range, 5 to 50 for positive affect and for negative affect, with higher scores indicating a greater intensity of the affect),[22] and the PHQ-9 depression score.[23] Every 3 months, participants were asked about their general

impression of the change in sexual desire, walking ability, or energy (depending on the trial) and in overall health.

STATISTICAL ANALYSIS

Participants were evaluated according to the intention-to-treat principle. Each outcome was prespecified. Primary analyses of outcomes at all time points were performed with random-effects models for longitudinal data. Models included visit time as a categorical variable and a single main effect for treatment. For linear models of continuous outcomes, the treatment effect denoted the average difference in response between study groups across all four visits. For logistic models of binary outcomes, the treatment effect was the log odds ratio of a positive versus negative outcome for participants who received testosterone versus those who received placebo, averaged over all visits. Additional fixed effects were the baseline value for each outcome and balancing variables. Random intercepts were included for participant.

We analyzed the three trials as independent studies, without adjusting analyses of the primary outcomes for multiple comparisons. We also did not adjust the analyses of the primary and secondary outcomes within each trial for multiple comparisons, because the correlations among outcomes within a trial were expected to be very high, making such adjustment excessively conservative. Analyses of the primary outcomes that included all participants, however, were adjusted for multiple comparisons; we report the nominal P value only when it was lower than the threshold specified by the multiple-comparisons procedure.[24] The sensitivity of results to missing data was assessed with the use of pattern-mixture models[25] and shared random-effects models.[26] The effect of change in total testosterone level on primary outcomes was assessed with the use of instrumental variables by two-stage residual inclusion,[27] with study-group assignment as the instrument and change in testosterone level from baseline as the exposure of interest.

Sample sizes were calculated such that the studies would have 90% power, with the use of a two-sided test at a type I error rate of 0.05,[10] to detect the following differences between the placebo group and the testosterone group: 15% versus 30% in the proportion of men with an increase of at least 50 m in the 6-minute walking distance, 20% versus 35% in the proportion of men with an increase of at least 4 points in the FACIT–Fatigue score, and a difference in change of 0.75 in the PDQ-Q4 score. These differences were conservatively based on comparisons between baseline and 12 months. Enrollment targets were 275 men for the Sexual Function Trial, 366 for the Physical Function Trial, and 420 for the Vitality Trial.

RESULTS

PARTICIPANTS AND STUDY TREATMENT

We screened 51,085 men and enrolled 790 who met all the criteria (Fig. S1 in the Supplementary Appendix).[11] Relatively few men had a sufficiently low testosterone level to qualify; only 4700 of 21,940 men (21.4%) who had blood sampled qualified by the first

measurement and 1490 of 2163 men (68.9%) qualified by the second, for an overall inclusion rate by testosterone level of 14.7%.[11]

At baseline, the enrollees had unequivocally low serum testosterone concentrations according to criteria for healthy young men (Fig. S2 in the Supplementary Appendix). The participants had relatively high rates of coexisting conditions: 62.9% were obese, 71.6% had hypertension, and 14.7% had a history of myocardial infarction (Table S1 in the Supplementary Appendix). The two study groups, however, had similar rates of these and other coexisting conditions; other baseline characteristics were also similar in the two groups.

Of the 790 men who were enrolled, 705 completed 12 months of study treatment. The characteristics of men who completed 12 months and those who did not complete 12 months did not differ appreciably (Table S2 in the Supplementary Appendix).

Testosterone treatment increased the median testosterone concentration to the mid-normal range for young men and maintained that range during the treatment period (Fig. S2 in the Supplementary Appendix). A total of 91% of men assigned to testosterone maintained a mean testosterone concentration above the lower limit of the normal range from month 3 through month 12. Testosterone treatment also increased levels of free testosterone, estradiol, and dihydrotestosterone but did not increase levels of sex hormone–binding globulin (Fig. S2 in the Supplementary Appendix).

EFFICACY

Sexual Function Trial—Averaged over all follow-up visits, sexual activity, as determined by the PDQ-Q4 score, increased more with testosterone treatment than with placebo, both among men enrolled in the Sexual Function Trial (treatment effect [the mean difference in the change from baseline between participants assigned to testosterone and those assigned to placebo], 0.58; P<0.001) (Fig. 1A) and among all Testosterone Trials participants (treatment effect, 0.62; P<0.001) (Table 1). A greater increase in testosterone level during treatment was associated with a greater increment in the PDQ-Q4 score (P<0.001 by instrumental variable analysis) (Fig. S3 in the Supplementary Appendix). The response was somewhat less at month 12 (P = 0.08 for the interaction between time and treatment). Testosterone treatment was also associated with increased sexual desire according to the DISF-M-II (treatment effect, 2.93; P<0.001) and increased erectile function according to the IIEF (treatment effect, 2.64; P<0.001) (Table 1). Men in the testosterone group were more likely than those in the placebo group to report that their sexual desire had improved since the beginning of the trial (P<0.001) (Fig. S4 in the Supplementary Appendix).

Physical Function Trial—Among men enrolled in the Physical Function Trial, there were no significant differences between the testosterone group and the placebo group in the percentage of men whose 6-minute walking distance increased by at least 50 m (primary outcome) (odds ratio, 1.42; P = 0.20) (Fig. 1B), the change from baseline in the 6-minute walking distance (mean difference, 4.09 m; P = 0.28) (Table 2), or the percentage of men whose PF-10 score increased by at least 8 points (odds ratio, 1.34; P = 0.15); there was a significant between-group difference in the change from baseline in the PF-10 score (mean

difference, 2.75 points; P = 0.03) (Table 2). Among all Testosterone Trials participants, there was a significant between-group difference in all four measures: the percentage of men whose 6-minute walking distance increased by at least 50 m (odds ratio, 1.76; P = 0.003), the change from baseline in the 6-minute walking distance (mean difference, 6.69 m; P = 0.007), the percentage of men whose PF-10 score increased by at least 8 points (odds ratio, 1.50; P = 0.02), and the change from baseline in the PF-10 score (mean difference, 3.06 points; P = 0.002). Men who received testosterone were more likely than those who received placebo to perceive that their walking ability had improved since the beginning of the trial (P = 0.002) (Fig. S4 in the Supplementary Appendix).

Vitality Trial—Among men enrolled in the Vitality Trial, testosterone treatment showed no significant benefit over placebo with respect to vitality, as determined by an increase of at least 4 points in the FACIT–Fatigue score (primary outcome) (odds ratio, 1.23; P = 0.30) (Fig. 1C). However, there appeared to be a small effect on the change from baseline in the FACIT–Fatigue score that did not reach significance (mean difference, 1.21 points; P=0.06) (Table 3). In addition, a greater increase in testosterone level was associated with a greater increment in the score (P = 0.02 by instrumental variable analysis) (Fig. S3 in the Supplementary Appendix), and the effect of testosterone on the change from baseline in the score in the participants in the three trials combined was significant (P = 0.006). Among participants in the Vitality Trial, there were significant differences between the testosterone group and the placebo group in the SF-36 vitality score (mean difference, 2.41 points; P = 0.03), the PANAS positive affect score (mean difference, 0.47 points; P = 0.04), the PANAS negative affect score (mean difference, −0.49 points; P<0.001), and the PHQ-9 depression score (mean difference, −0.72 points; P = 0.004) (Table 3). The effect sizes (the mean between-group differences in outcome divided by the baseline standard deviations) were all below 0.20. The men who received testosterone were more likely than men who received placebo to report that their energy was better at the end of the trial (P<0.001) (Fig. S4 in the Supplementary Appendix).

All Trials—Sensitivity analyses of the primary outcomes did not suggest that missing values affected any conclusions appreciably (Table S3 in the Supplementary Appendix). We found no significant interactions of treatment with age (P values ranged from 0.45 to 0.78 in the three trials), body-mass index (P values ranged from 0.35 to 0.85), or race (P values ranged from 0.49 to 0.72).

ADVERSE EVENTS

Although more men assigned to testosterone than those assigned to placebo had an increment in the PSA level of 1.0 ng per milliliter or more during the treatment period (23 vs. 8), only 1 man (in the testosterone group) received a diagnosis of prostate cancer during that time. Two men in the testosterone group and 1 in the placebo group received a diagnosis during the subsequent year (Table 4, and Table S4 in the Supplementary Appendix). The change in the IPSS did not differ significantly between the two groups. A hemoglobin level of 17.5 g per deciliter or more was observed in 7 men in the testosterone group and none in the placebo group.

Seven men in each study group were adjudicated to have had major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) during the treatment period and two men in the testosterone group and nine men in the placebo group were adjudicated to have had major cardiovascular events during the subsequent year (Table 4, and Table S4 in the Supplementary Appendix). There was no pattern of a difference in risk with respect to the other cardiovascular adverse events (Table S4 in the Supplementary Appendix). No significant between-group differences were observed in cardiac adverse events defined according to *Medical Dictionary for Regulatory Activities* classification (Tables S5 and S6 in the Supplementary Appendix).

DISCUSSION

Increasing the serum testosterone concentrations of men 65 years of age or older from moderately low to the mid-normal range for men 19 to 40 years of age had significant effects on all measures of sexual function and some measures of physical function, mood, and depressive symptoms — all to small-to-moderate degrees, consistent with the degree of testosterone deficiency.

Men who received testosterone reported better sexual function, including activity, desire, and erectile function, than those who received placebo. Although the effect sizes were low to moderate, men in the testosterone group were more likely than those in the placebo group to report that their sexual desire had improved, which suggests that this effect was of clinical relevance. The effect of testosterone on erectile function was less than that reported with phosphodiesterase type 5 inhibitors.[28]

The percentage of men whose 6-minute walking distance increased by at least 50 m did not differ significantly between the two study groups in the Physical Function Trial but did differ significantly when men in all three trials were included, although the effect sizes did not differ markedly (1.42 vs. 1.76). Furthermore, men who received testosterone were more likely than those who received placebo to report that their walking ability was better, which suggests that the effect, although small in magnitude, might be clinically relevant.

Testosterone had no significant benefit with respect to vitality, as assessed by the FACIT–Fatigue scale, except as a continuous outcome when men in all three trials were included. However, testosterone was associated with small but significant benefits with respect to mood and depressive symptoms. Men in the testosterone group were also more likely than those in the placebo group to report that their energy was better.

We observed four cases of prostate cancer, three of which were in men treated with testosterone, and there was no significant difference in urinary symptoms (as assessed by means of the IPSS) between the study groups. The generalizability of these results is limited, however, because we excluded men with a high risk of prostate cancer and men with moderately severe urinary tract symptoms. Furthermore, the sample size was inadequate to assess reliably the effect of testosterone on the risk of these conditions.

Some studies have suggested that testosterone treatment is associated with increased cardiovascular risk,[29–32] although others have not.[6,33,34] We did not observe a pattern of increased risk, but this trial was too small to exclude other than a large increase.

Our three trials had certain strengths, including enrollment of men with an unequivocally low mean testosterone concentration, adequate sample sizes, a double-blind, placebo-controlled design, an increase in serum testosterone concentration to the normal range for young men, and excellent participant retention. A major limitation, albeit an intentional one, is that the results apply only to men 65 years of age or older whose testosterone levels averaged less than 275 ng per deciliter.

Results of the primary outcomes in our three trials showed that testosterone treatment had a moderate, significant benefit with respect to sexual function but no significant benefit with respect to walking distance (among participants in the Physical Function Trial) or vitality. Testosterone treatment also had a significant benefit with respect to other prespecified outcomes, including walking distance when men in all three trials were included and mood and depressive symptoms. These results, together with those of the other four trials (now completed), should inform decisions about testosterone treatment for men 65 years of age or older whose levels are low for no apparent reason other than age. Such decisions will also require knowing the risks of testosterone treatment, which will necessitate larger and longer trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

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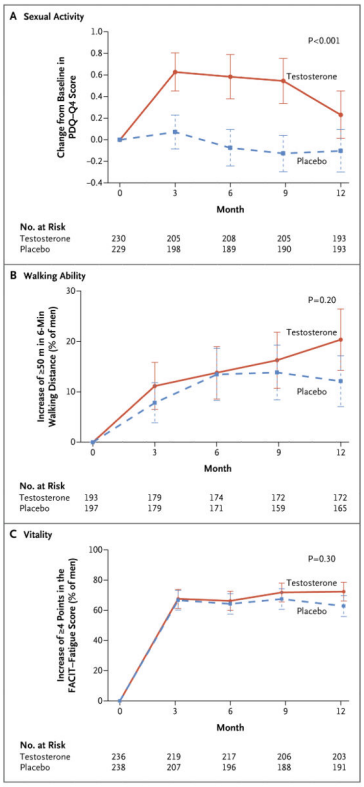

Figure 1. Primary Outcomes in the Three Main Trials of the Testosterone Trials

The primary outcome of the Sexual Function Trial (Panel A) was the change from baseline in the score for sexual activity (question 4) on the Psychosexual Daily Questionnaire (PDQ-Q4; range, 0 to 12, with higher scores indicating more activity). The primary outcome of the Physical Function Trial (Panel B) was the percentage of men who had an increase of at least 50 m in the distance walked during the 6-minute walk test. The primary outcome of the Vitality Trial (Panel C) was the percentage of men who had an increase of at least 4 points in the score on the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale (range, 0 to 52, with higher scores indicating less fatigue). P values were calculated with the use of a linear random-effects model for sexual activity and logistic random-effects models for walking ability and vitality. The I bars represent standard deviations.

Table 1

Sexual Function Trial Outcomes.*

Cohort and Outcome	No. of Men	Baseline Value	Change from Baseline Value				Treatment Effect (95% CI)†	Effect Size (95% CI)‡	P Value§
			Month 3	Month 6	Month 9	Month 12			
Men enrolled in Sexual Function Trial									
Primary outcome: PDQ-Q4 score¶									
Testosterone	230	1.4±1.3	0.6±1.3	0.6±1.5	0.5±1.5	0.2±1.6	0.58 (0.38–0.78)	0.45 (0.30–0.60)	<0.001
Placebo	229	1.4±1.3	0.1±1.1	−0.1±1.2	−0.1±1.2	−0.1±1.4			
Secondary outcomes									
DISF-M-II sexual desire score‖									
Testosterone	234	11.9±6.7	3.5±6.3	3.5±6.0	4.0±7.4	2.6±6.5	2.93 (2.13–3.74)	0.44 (0.32–0.56)	<0.001
Placebo	236	11.6±6.6	0.7±5.8	0.8±5.6	0.9±5.5	0.0±5.0			
IIEF erectile function score**									
Testosterone	234	8.0±8.2	3.4±6.1	3.3±6.5	3.4±6.9	3.1±6.9	2.64 (1.68–3.61)	0.32 (0.20–0.44)	<0.001
Placebo	236	7.7±8.2	1.0± 5.3	0.5±6.1	0.5±7.1	1.0±6.0			
All Testosterone Trials participants††									
PDQ-Q4 score¶									
Testosterone	387	1.5±1.3	0.7±1.3	0.6±1.6	0.6±1.6	0.3±1.7	0.62 (0.45–0.79)	0.45 (0.33–0.58)	<0.001
Placebo	384	1.5±1.4	0.0±1.2	−0.1±1.3	−0.1±1.3	−0.1±1.4			

*Plus–minus values are means ±SD.

†The treatment effect is the mean difference in change from baseline for participants assigned to testosterone versus those assigned to placebo, with adjustment for balancing factors: baseline total testosterone level (≤200 or >200 ng per deciliter), age (≤75 or >75 years), trial site, participation in the main trials, use or nonuse of antidepressants, and use or nonuse of phosphodiesterase type 5 inhibitors.

‡The effect size is the treatment effect divided by the baseline standard deviation.

§The P value for the treatment effect was determined with the use of a linear mixed model with a random effect for participant.

¶Scores for sexual activity (question 4) on the Psychosexual Daily Questionnaire (PDQ-Q4) range from 0 to 12, with higher scores indicating more activity.

‖Scores on the sexual-desire domain of the Derogatis Interview for Sexual Functioning in Men–II (DISF-M-II) range from 0 to 33, with higher scores indicating greater desire.

**Scores on the erectile-function domain of the International Index of Erectile Function (IIEF) range from 0 to 30, with higher scores indicating better function.

††The outcomes for all Testosterone Trials participants are exploratory outcomes.

Table 2

Physical Function Trial Outcomes.*

Cohort and Outcome	No. of Men	Baseline Value	No. of Participants or Change from Baseline Value				Treatment Effect (95% CI)†	Effect Size (95% CI)‡	P Value§
			Month 3	Month 6	Month 9	Month 12			
Men enrolled in Physical Function Trial									
Primary outcome: increase of ≥ 50 m in 6-min walk test — no./ total no. (%)									
Testosterone	191		20/179 (11.2)	24/174 (13.8)	28/172 (16.3)	35/172 (20.3)	1.42 (0.83 to 2.45)		0.20
Placebo	196		14/179 (7.8)	23/171 (13.5)	22/159 (13.8)	20/165 (12.1)			
Secondary outcomes									
6-Min walking distance — m									
Testosterone	191	347.7±69.1	10.2±35.8	8.2±41.5	5.3±50.3	14.3±45.9	4.09 (−3.00 to 11.18)	0.06 (−0.04 to 0.16)	0.28
Placebo	196	344.9±68.5	4.6±35.2	7.8±41.4	3.2±52.4	5.5±46.4			
Increase of ≥8 in PF-10 score — no./total no. (%)¶									
Testosterone	184		77/176 (43.8)	72/171 (42.1)	77/172 (44.8)	66/173 (38.2)	1.34 (0.90 to 2.00)		0.15
Placebo	181		59/171 (34.5)	73/159 (45.9)	60/159 (37.7)	58/167 (34.7)			
PF-10 score¶									
Testosterone	184	65.4±20.0	5.6±15.2	6.5±16.7	5.9±19.4	5.8±17.5	2.75 (0.20 to 5.29)	0.13 (0.01 to 0.26)	0.03
Placebo	181	64.8±21.3	4.2±13.7	4.8±17.0	3.3±18.9	2.4±17.3			
All Testosterone Trials participants‖									
Increase of ≥ 50 m in 6-min walk test — no./total no. (%)									
Testosterone	392		40/368 (10.9)	52/358 (14.5)	54/348 (15.5)	71/346 (20.5)	1.76 (1.21 to 2.57)		0.003
Placebo	389		25/356 (7.0)	39/339 (11.5)	37/320 (11.6)	41/326 (12.6)			
6-Min walking distance — m									
Testosterone	392	387.0±81.7	10.9±45.1	11.0±40.2	6.7±45.1	13.6±43.4	6.69 (1.80 to 11.57)	0.08 (0.02 to 0.14)	0.007
Placebo	389	387.0±83.7	1.6±41.9	5.7±45.1	3.2±47.4	6.4±45.8			
Increase of ≥ 8 in PF-10 score — no./total no. (%)¶									

Cohort and Outcome	No. of Men	Baseline Value	No. of Participants or Change from Baseline Value				Treatment Effect (95% CI)†	Effect Size (95% CI)‡	P Value§
			Month 3	Month 6	Month 9	Month 12			
Testosterone	309		111/285 (38.9)	113/281 (40.2)	115/276 (41.7)	103/281 (36.7)	1.50 (1.08 to 2.09)		0.02
Placebo	305		87/275 (31.6)	103/263 (39.2)	89/260 (34.2)	82/272 (30.1)			
PF-10 score¶									
Testosterone	309	71.2±20.2	5.0±14.7	6.1±16.7	5.3±18.5	4.3±16.9	3.06 (1.18 to 4.94)	0.15 (0.06 to 0.24)	0.002
Placebo	305	69.7±21.2	3.9±12.8	3.4±16.2	2.3±17.9	1.3±16.9			

*Plus–minus values are means ±SD.

†The treatment effect for dichotomous outcomes is the odds ratio for achieving the outcome versus not achieving the outcome among men assigned to testosterone versus those assigned to placebo. For continuous outcomes, the treatment effect is the mean difference in the outcome among men assigned to testosterone versus those assigned to placebo. All analyses are adjusted for balancing factors: baseline total testosterone level (≤200 or >200 ng per deciliter), age (≤75 or >75 years), trial site, participation in the main trials, use or non-use of antidepressants, and use or nonuse of phosphodiesterase type 5 inhibitors.

‡For continuous outcomes, the effect size is the treatment effect divided by the baseline standard deviation.

§The P value for the treatment effect was determined with the use of a logistic mixed model with a random effect for participant for dichotomous outcomes and a linear mixed model with a random effect for participant for continuous outcomes.

¶Scores on the physical-function scale (PF-10) of the Medical Outcomes Study 36-Item Short-Form Health Survey range from 0 to 100, with higher scores indicating better function.

//The outcomes for all Testosterone Trials participants are exploratory outcomes.

Table 3

Vitality Trial Outcomes.*

Cohort and Outcome	No. of Men	Baseline Value	No. of Participants or Change from Baseline Value				Treatment Effect (95% CI)†	Effect Size (95% CI)‡	P Value§
			Month 3	Month 6	Month 9	Month 12			
Men enrolled in Vitality Trial									
Primary outcome: increase of ≥4 in FACIT– Fatigue score — no./total no. (%)¶									
Testosterone	236		148/219 (67.6)	144/217 (66.4)	148/206 (71.8)	147/203 (72.4)	1.23 (0.83 to 1.84)		0.30
Placebo	238		138/207 (66.7)	126/196 (64.3)	127/188 (67.6)	120/191 (62.8)			
Secondary outcomes									
FACIT–Fatigue score¶									
Testosterone	236	31.6±6.4	7.7±8.4	7.4±9.1	8.6±9.1	8.0±8.4	1.21 (−0.04 to 2.46)	0.19 (0.01 to 0.38)	0.06
Placebo	238	31.3±6.4	7.2±8.8	5.9±9.2	7.2±9.2	6.7±9.4			
SF-36 vitality score‖									
Testosterone	208	50.6±13.8	7.4±13.6	7.2±14.6	8.4±14.4	8.2±15.3	2.41 (0.31 to 4.50)	0.18 (0.02 to 0.34)	0.03
Placebo	196	49.4±12.6	5.9±11.1	4.5±11.2	5.7±12.3	6.1±13.8			
PANAS positive affect score**									
Testosterone	229	15.3±3.2	0.7±3.2	0.9±3.8	0.9±3.4	0.7±3.9	0.47 (0.02 to 0.92)	0.14 (0.01 to 0.27)	0.04
Placebo	234	15.4±3.5	0.3±3.3	0.0±3.3	0.4±3.4	0.2±3.2			
PANAS negative affect score**									
Testosterone	229	7.5±2.7	−0.2±2.5	−0.4±2.4	−0.2±2.3	−0.6±2.1	−0.49 (−0.79 to −0.19)	−0.18 (−0.29 to −0.06)	<0.001
Placebo	234	7.4±2.8	0.3±2.4	0.4±2.6	−0.1±2.6	−0.1±2.6			
PHQ-9 depression score††									
Testosterone	230	6.6±4.0	−1.3±3.8	−1.7±3.8	−1.9±4.0	−1.8±3.7	−0.72 (−1.20 to −0.23)	−0.18 (−0.30 to −0.06)	0.004
Placebo	234	6.6±4.0	−0.8±3.5	−0.5±3.7	−1.2±4.2	−1.1±3.8			
All Testosterone Trials participants‡‡									

Cohort and Outcome	No. of Men	Baseline Value	No. of Participants or Change from Baseline Value				Treatment Effect (95% CI)†	Effect Size (95% CI)‡	P Value§
			Month 3	Month 6	Month 9	Month 12			
Increase of ≥4 in FACIT–Fatigue score — no./total no. (%)¶									
Testosterone	394		176/351 (50.1)	181/350 (51.7)	178/337 (52.8)	174/333 (52.3)	1.23 (0.89 to 1.70)		0.22
Placebo	394		166/337 (49.3)	151/329 (45.9)	154/317 (48.6)	152/316 (48.1)			
FACIT–Fatigue score¶									
Testosterone	394	37.0±8.6	4.7±8.5	4.8±8.7	5.2±9.1	4.7±8.8	1.27 (0.37 to 2.16)	0.15 (0.04 to 0.25)	0.006
Placebo	394	36.8±8.8	4.1±9.0	2.8±9.0	3.7±9.2	3.6±9.5			

* Plus–minus values are means ±SD.

† The treatment effect for dichotomous outcomes is the odds ratio for achieving the outcome versus not achieving the outcome among men assigned to testosterone versus those assigned to placebo. For continuous outcomes, the treatment effect is the mean difference in the outcome among men assigned to testosterone versus those assigned to placebo. All analyses are adjusted for balancing factors: baseline total testosterone level (≤200 or >200 ng per deciliter), age (≤75 or >75 years), trial site, participation in the main trials, use or nonuse of antidepressants, and use or nonuse of phosphodiesterase type 5 inhibitors.

‡ For continuous outcomes, the effect size is the treatment effect divided by the baseline standard deviation.

§ The P value for the treatment effect was determined with the use of a logistic mixed model with a random effect for participant for dichotomous outcomes and a linear mixed model with a random effect for participant for continuous outcomes.

¶ Scores on the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale range from 0 to 52, with higher scores indicating less fatigue.

‖ Scores on the vitality scale of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating more vitality.

** Scores for positive affect and for negative affect on the Positive and Negative Affect Schedule (PANAS) scales range from 5 to 50, with higher scores indicating a greater intensity of the affect.

†† Scores on the Patient Health Questionnaire 9 (PHQ-9) depression scale range from 0 to 27, with higher scores indicating greater intensity of depressive symptoms.

‡‡ The outcomes for all Testosterone Trials participants are exploratory outcomes.

Table 4

Adverse Events during the First Year (Treatment Period) of the Testosterone Trials.*

Event	Placebo (N = 394)	Testosterone (N = 394)
	no. of participants	
Prostate-related event		
Increase in PSA level by ≥1.0 ng/ml	8	23
Prostate cancer	0	1
IPSS >19†	26	27
Hemoglobin ≥17.5 g/dl	0	7
Cardiovascular event‡		
Myocardial infarction (definite or probable)	1	2
Stroke (definite or probable)	5	5
Death from cardiovascular causes	1	0
Myocardial infarction, stroke, or death from cardiovascular causes	7	7
Serious adverse events		
Death	7	3
Hospitalization	78	68
Other§	6	7

*PSA denotes prostate-specific antigen.

†The International Prostate Symptom Score (IPSS) questionnaire is used to identify symptoms of benign prostatic hyperplasia. Scores range from 0 to 35, with higher scores indicating more severe symptoms. A score of more than 19 indicates moderately severe lower urinary tract symptoms.

‡Data on cardiovascular adverse events were collected with the use of a specific questionnaire administered at each visit and also identified from the adverse-event log and the form for reporting serious adverse events (see the protocol). Myocardial infarction, stroke, and death from cardiovascular causes were assessed by two adjudicators.

§Other serious adverse events were defined as congenital anomaly, disability, a life-threatening event, or an event that may not be immediately life-threatening but is clearly of major clinical significance.