The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 13, 2023 VOL. 389 NO. 2

Cardiovascular Safety of Testosterone-Replacement Therapy

A.M. Lincoff, S. Bhasin, P. Flevaris, L.M. Mitchell, S. Basaria, W.E. Boden, G.R. Cunningham, C.B. Granger, M. Khera, I.M. Thompson, Jr., Q. Wang, K. Wolski, D. Davey, V. Kalahasti, N. Khan, M.G. Miller, M.C. Snabes, A. Chan, E. Dubcenco, X. Li, T. Yi, B. Huang, K.M. Pencina, T.G. Travison, and S.E. Nissen, for the TRAVERSE Study Investigators*

ABSTRACT

BACKGROUND

The cardiovascular safety of testosterone-replacement therapy in middle-aged and older men with hypogonadism has not been determined.

METHODS

In a multicenter, randomized, double-blind, placebo-controlled, noninferiority trial, we enrolled 5246 men 45 to 80 years of age who had preexisting or a high risk of cardiovascular disease and who reported symptoms of hypogonadism and had two fasting testosterone levels of less than 300 ng per deciliter. Patients were randomly assigned to receive daily transdermal 1.62% testosterone gel (dose adjusted to maintain testosterone levels between 350 and 750 ng per deciliter) or placebo gel. The primary cardiovascular safety end point was the first occurrence of any component of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, assessed in a time-to-event analysis. A secondary cardiovascular end point was the first occurrence of any component of the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, assessed in a time-to-event analysis. Noninferiority required an upper limit of less than 1.5 for the 95% confidence interval of the hazard ratio among patients receiving at least one dose of testosterone or placebo.

RESULTS

The mean (±SD) duration of treatment was 21.7±14.1 months, and the mean follow-up was 33.0±12.1 months. A primary cardiovascular end-point event occurred in 182 patients (7.0%) in the testosterone group and in 190 patients (7.3%) in the placebo group (hazard ratio, 0.96; 95% confidence interval, 0.78 to 1.17; P<0.001 for noninferiority). Similar findings were observed in sensitivity analyses in which data on events were censored at various times after discontinuation of testosterone or placebo. The incidence of secondary end-point events or of each of the events of the composite primary cardiovascular end point appeared to be similar in the two groups. A higher incidence of atrial fibrillation, of acute kidney injury, and of pulmonary embolism was observed in the testosterone group.

CONCLUSIONS

In men with hypogonadism and preexisting or a high risk of cardiovascular disease, testosterone-replacement therapy was noninferior to placebo with respect to the incidence of major adverse cardiac events. (Funded by AbbVie and others; TRAVERSE ClinicalTrials.gov number, NCT03518034.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Nissen can be contacted at nissens@ccf.org or at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195.

*A list of the TRAVERSE Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Lincoff and Bhasin contributed equally to this article.

This article was published on June 16, 2023, at NEJM.org.

N Engl J Med 2023;389:107-17.
DOI: 10.1056/NEJMoa2215025

CME at NEJM.org

A Quick Take is available at NEJM.org

The cardiovascular effects of testosterone-replacement therapy in middle-aged and older men with hypogonadism have not been determined. Retrospective cohort studies involving men receiving testosterone-replacement therapy have shown conflicting results, with some showing increased and others decreased cardiovascular risk.[1-5] Small randomized trials similarly have not shown a consistent association of testosterone treatment with cardiovascular risk, although none were designed to systematically assess cardiovascular outcomes and all were inadequately powered and had a short duration.[6-10]

In response to concerns and conflicting data regarding the cardiovascular safety of testosterone-replacement therapy, the Food and Drug Administration (FDA) issued a guidance on March 3, 2015, that required manufacturers of approved testosterone products to conduct clinical trials to determine whether testosterone-replacement therapy is associated with an increased risk of cardiovascular events.[11] The Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial was designed to determine the effects of testosterone-replacement therapy on the incidence of major adverse cardiac events among middle-aged and older men with hypogonadism and either preexisting or a high risk of cardiovascular disease.

Methods

Trial Design and Oversight

We conducted this phase 4, randomized, double-blind, placebo-controlled, noninferiority, event-driven trial at 316 clinical-trial sites in the United States (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial design has been published previously.[12] The trial was funded by a consortium of testosterone manufacturers led by AbbVie and was overseen by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) with support from a contract research organization (Labcorp Drug Development). The trial protocol, available at NEJM.org, was designed by the executive committee and sponsor. National and institutional regulatory and ethical authorities approved the protocol, and all the patients provided written informed consent. An independent data and safety monitoring committee reviewed unblinded safety data. The clinical database was maintained by Labcorp Drug Development and transferred to C5Research for independent statistical analyses.

The first author wrote the first draft of the manuscript, which was reviewed and approved by all the authors. The sponsor reviewed the manuscript and provided suggested revisions, but the final decision regarding content was reserved for the academic authors, with no restrictions on the right to publish. The first and last authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and the statistical analysis plan.

Trial Population

Men with preexisting cardiovascular disease or an elevated cardiovascular risk were eligible if they were 45 to 80 years of age; reported one or more symptoms of hypogonadism, including decreased sexual desire or libido, decreased spontaneous erections, fatigue or decreased energy, low or depressed mood, loss of axillary or pubic body hair or decreased frequency of shaving, or hot flashes; and had two fasting serum testosterone levels of less than 300 ng per deciliter (10.4 nmol per liter) in blood samples obtained between 5:00 a.m. and 11:00 a.m. and measured at a central laboratory with the use of liquid chromatography–tandem mass spectrometry.

Cardiovascular disease was defined as clinical or angiographic evidence of coronary artery disease, cerebrovascular disease, or peripheral arterial disease. Increased cardiovascular risk was defined as the presence of three or more of the following risk factors: hypertension, dyslipidemia, current smoking, stage 3 chronic kidney disease, diabetes, elevated high-sensitivity C-reactive protein level, age of 65 years or older, or an Agatston coronary calcium score that was above the 75th percentile for age and race.

Exclusion criteria included congenital or acquired severe hypogonadism (testosterone level, <100 ng per deciliter [3.5 nmol per liter]), a history of prostate cancer or prostate nodules, an elevated screening prostate-specific antigen (PSA) level, thrombophilia, and uncontrolled heart failure. Patients could not be enrolled within 4 months after an acute coronary syndrome, stroke, or coronary or peripheral revascularization or within 6 months after treatment with testosterone or

androgenic steroids. Detailed eligibility criteria are provided in the Supplementary Appendix.

TRIAL INTERVENTION

Patients were randomly assigned in a 1:1 ratio to receive daily transdermal 1.62% testosterone gel or matching placebo gel provided in metered-dose pumps. Randomization was stratified according to the presence or absence of preexisting cardiovascular disease. To avoid unblinding, the patients and trial team remained unaware of the post-baseline testosterone levels measured at the central laboratory. Dose adjustments to maintain testosterone levels between 350 and 750 ng per deciliter (12.1 to 26.0 nmol per liter) or to respond to a hematocrit greater than 54% were managed centrally by an automated algorithm (additional details are provided in the Supplementary Appendix). Patients who were randomly assigned to placebo underwent sham adjustments to maintain blinding.

Testosterone or placebo was discontinued in patients with testosterone levels that exceeded 750 ng per deciliter or with a hematocrit that exceeded 54% even after adjustment to the lowest dose, as well as in patients who had a new diagnosis of prostate cancer or were deemed to be at risk for suicide; otherwise, the assigned intervention was to be continued for the duration of the trial. The investigators received specific guidelines regarding care or referral to a urologist for patients with an elevated PSA level.

END POINTS

The primary safety end point was the first occurrence of any component of major adverse cardiac events, a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis. A secondary cardiovascular end point was the first occurrence of any component of the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization in a time-to-event analysis. Tertiary end points included death from any cause, hospitalization or an urgent visit for heart failure, peripheral arterial revascularization, and venous thromboembolic events. An independent clinical-events committee whose members were unaware of the trial-group assignments adjudicated all cardiovascular end points. Definitions of the end points are provided in the Supplementary Appendix. Effects of testosterone therapy on noncardiovascular outcomes in this trial are not reported in this article (see Table S1 in the Supplementary Appendix).

STATISTICAL ANALYSIS

In this noninferiority trial, we used a Cox proportional-hazards regression model to estimate the hazard ratio and its two-sided 95% confidence interval for a primary end-point event with testosterone as compared with placebo, with adjustment for preexisting cardiovascular disease. The trial was designed to conclude after 256 primary composite end-point events had occurred. This number of events would provide 90% power to detect an upper limit of less than 1.5 for the 95% confidence interval of the hazard ratio (one-sided alpha level, 2.5%). Because the statistical analysis plan did not include a provision for correcting for multiplicity for tests of secondary or other end points, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary end points.

The full-analysis population consisted of all the patients who had undergone randomization, and the safety population consisted of all the patients who had undergone randomization and had received at least one dose of testosterone or placebo. The primary analysis involved the safety population and was repeated in a supportive analysis involving the full-analysis population. The principal sensitivity analysis included major adverse cardiac events that occurred during the period from randomization to 365 days after the last dose, with censoring of data on events that occurred more than 365 days after the last dose. Additional sensitivity and supportive analyses based on different event censoring times and a restricted mean survival time at 3 years are described in the Supplementary Appendix.

Under the assumption of an annual event rate for the primary end point of 1.5% in the placebo group, with an accrual period of 3.5 years and an annualized loss to follow-up rate of 2%, the sample size was estimated to be approximately 5400 patients to observe the required 256 events. However, to achieve similar power for the principal sensitivity analysis, the required sample size was estimated to be approximately 6000 patients,

Table 1. Baseline Characteristics of Patients in the Full-Analysis Population.*

Characteristic	Testosterone Group (N=2601)	Placebo Group (N=2603)
Mean age — yr	63.3±7.9	63.3±7.9
Age ≥65 yr — no. (%)	1241 (47.7)	1211 (46.5)
Race or ethnic group — no. (%)†		
White	2070 (79.6)	2084 (80.1)
Black	445 (17.1)	432 (16.6)
Other	86 (3.3)	87 (3.3)
Hispanic or Latinx	409 (15.7)	439 (16.9)
Body-mass index‡	35.0±5.7	34.8±6.0
Median testosterone level (IQR) — ng/deciliter	227 (189–258)	227 (188–258)
Cardiovascular risk category — no. (%)		
Preexisting cardiovascular disease	1410 (54.2)	1437 (55.2)
Increased cardiovascular risk	1191 (45.8)	1166 (44.8)
History of coronary artery disease — no. (%)	1158 (44.5)	1160 (44.6)
History of cerebrovascular disease — no. (%)	304 (11.7)	318 (12.2)
History of peripheral arterial disease — no. (%)	158 (6.1)	153 (5.9)
Cardiovascular risk factors — no. (%)		
Diabetes, type 1 or type 2	1788 (68.7)	1844 (70.8)
Hypertension	2423 (93.2)	2402 (92.3)
Dyslipidemia	2344 (90.1)	2332 (89.6)
Current smoker	527 (20.3)	534 (20.5)
High-sensitivity C-reactive protein level ≥2 mg/dl	1607 (61.8)	1589 (61.0)
Stage 3 chronic kidney disease	418 (16.1)	393 (15.1)
Elevated coronary calcium score	29 (1.1)	28 (1.1)
Previous testosterone use — no. (%)	5 (0.2)	10 (0.4)
Medication — no. (%)		
Lipid-lowering therapy	2185 (84.0)	2180 (83.7)
Aspirin	1571 (60.4)	1550 (59.5)
Phosphodiesterase-5 inhibitor	170 (6.5)	189 (7.3)
Prostate-specific antigen level — ng/ml	0.91±0.65	0.94±0.68
Hematocrit — %	42±4	42±4
Lipid levels — mg/dl		
HDL cholesterol	41.9±11.2	41.7±10.9
LDL cholesterol	80.2±34.0	79.3±33.9
Median triglycerides (IQR)	154.6 (108.1–227.6)	157.7 (112.5–226.7)

* Plus–minus values are means ±SD. The full-analysis population consisted of all patients who had undergone randomization. To convert the values for high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for serum total testosterone to nanomoles per liter, divide by 28.84. IQR denotes interquartile range.
† Race and ethnic group were reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

on the assumption of a testosterone or placebo discontinuation rate of 20% in the first year and 10% in each subsequent year. To reach the intended event rate for the primary end point, the protocol allowed the executive committee and sponsor to limit enrollment in the cohort with cardiovascular risk factors if that cohort exceeded 70% of the total enrollment or if the pooled primary event rate fell below projections. All statistical analyses were performed with the use of SAS software, version 9.4.

RESULTS

PATIENTS

The first patient was enrolled on May 23, 2018. A total of 5246 patients underwent randomization, and 20 patients were excluded from the full-analysis population owing to duplicate enrollment involving a total of 42 patient identification numbers (Fig. S1). Of the 5204 patients in the full-analysis population, 2601 were assigned to receive testosterone and 2603 were assigned to receive placebo. The safety population included 5198 patients who had received at least one dose of testosterone or placebo (2596 patients in the testosterone group and 2602 in the placebo group).

In April 2019, blinded data from the first 2669 patients showed a pooled primary event rate below the projected rate of 1.5% per year. Therefore, on May 31, 2019, the executive committee and sponsor discontinued enrollment of patients who qualified on the basis of cardiovascular risk factors and thereafter enrolled only those with preexisting cardiovascular disease. Subsequently, on the basis of blinded assessments of pooled accrual rates of major adverse cardiac events, enrollment was terminated on February 1, 2022, and end-of-trial visits began after May 31, 2022. At the completion of follow-up, 372 adjudicated primary end-point events had occurred, and 306 primary end-point events qualified for the principal sensitivity analysis.

Baseline characteristics are summarized in Table 1. The trial included 2847 patients with preexisting cardiovascular disease and 2357 patients at elevated cardiovascular risk. The baseline median serum testosterone level was 227 ng per deciliter; interquartile range, 188 to 258 (7.8 nmol per liter; interquartile range, 6.5 to 8.9) in the combined trial groups. The demographic characteristics were representative of the population of middle-aged and older men with hypogonadism and a high risk of cardiovascular events (Table S2).

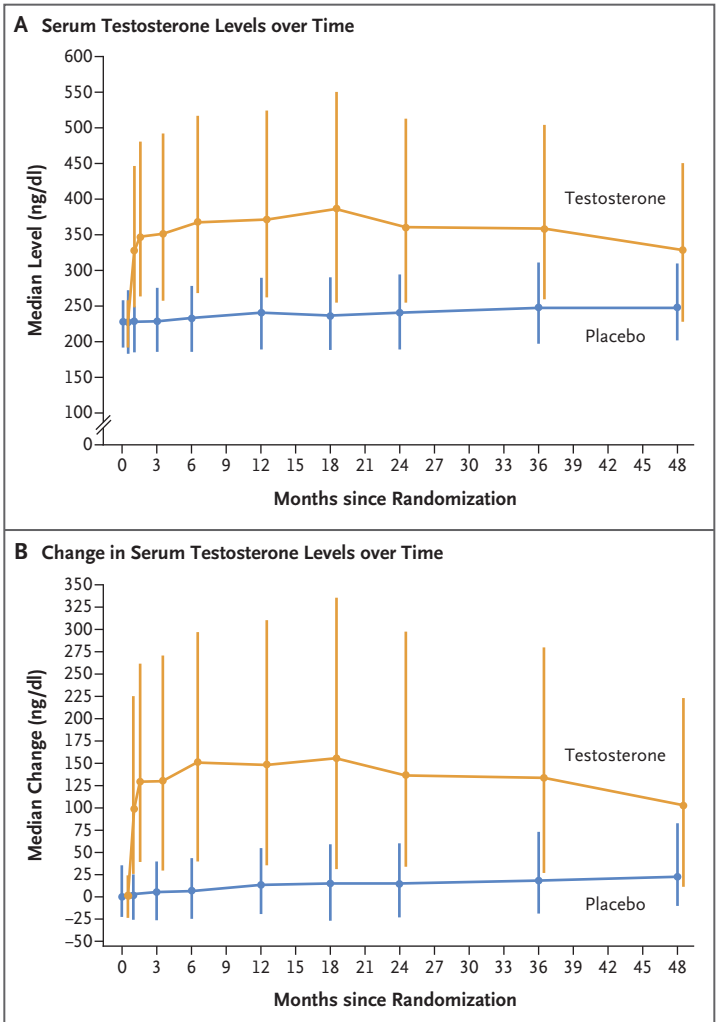
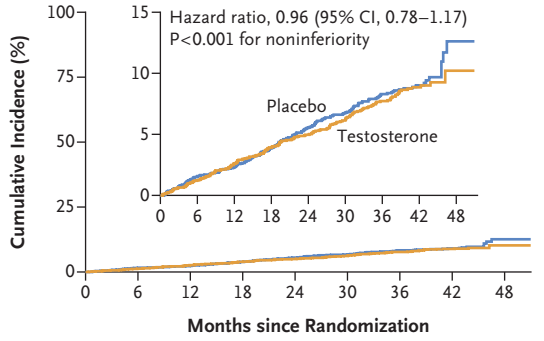


Figure 1. Median Serum Testosterone Levels and Changes in Serum Testosterone Levels over Time.

Shown are median serum testosterone levels (Panel A) and changes from baseline in serum testosterone levels over time since randomization (Panel B). Blood samples were collected 24 hours (±2 hours) after the patient received a dose of testosterone or placebo, preferably in the morning. Vertical bars represent interquartile ranges. To convert serum total testosterone levels to nanomoles per liter, divide by 28.84.

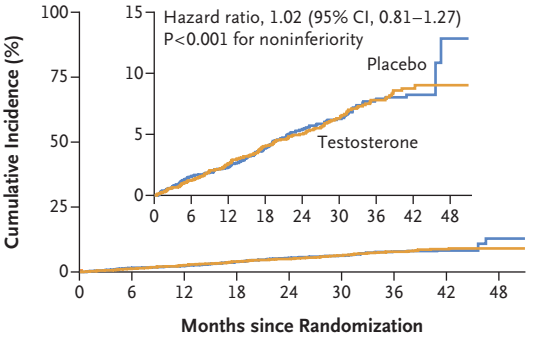
The mean (±SD) durations of treatment and follow-up, respectively, were 21.8±14.2 and 33.1±12.0 months in the testosterone group and 21.6±14.0 and 32.9±12.1 months in the placebo group. A total of 61.4% of the patients in the testosterone group discontinued testosterone, and 61.7% of the patients in the placebo group

A Primary Cardiovascular Composite Safety End Point: Safety Population



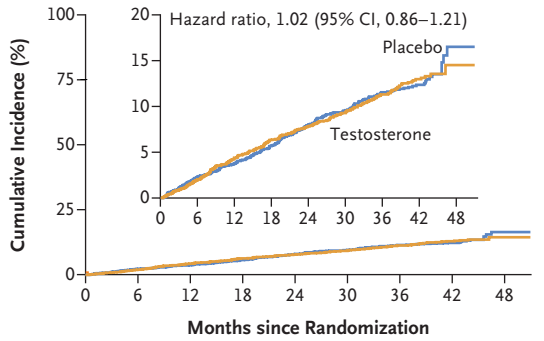
No. at Risk									
Placebo	2602	2507	2323	2088	1792	1568	1337	598	33
Testosterone	2596	2504	2339	2120	1829	1605	1380	653	39

B Primary Cardiovascular Composite Safety End Point: Principal Sensitivity Analysis Population



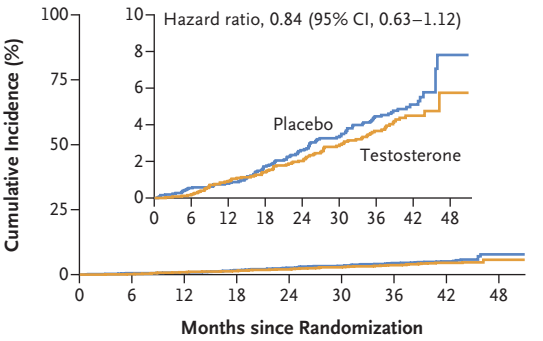
No. at Risk									
Placebo	2602	2507	2323	1842	1390	1070	829	347	16
Testosterone	2596	2504	2339	1850	1408	1089	850	370	20

C Secondary Cardiovascular Composite Safety End Point: Safety Population



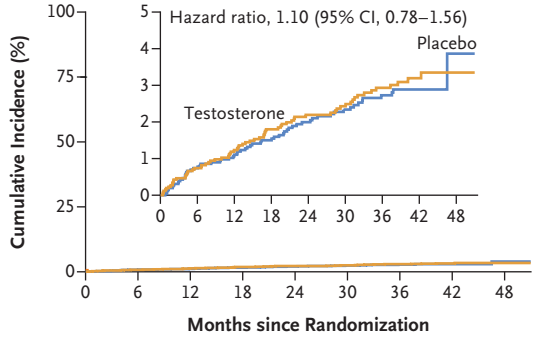
No. at Risk									
Placebo	2602	2488	2289	2048	1747	1522	1293	575	31
Testosterone	2596	2484	2295	2065	1776	1555	1330	625	37

D Death from Cardiovascular Causes: Safety Population



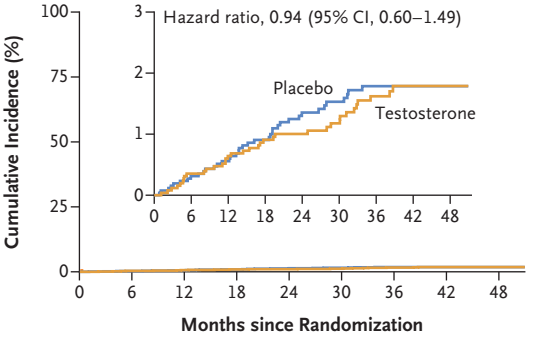
No. at Risk									
Placebo	2602	2533	2360	2130	1845	1624	1390	619	34
Testosterone	2596	2529	2375	2167	1875	1647	1423	672	40

E Nonfatal Myocardial Infarction: Safety Population



No. at Risk									
Placebo	2602	2515	2335	2104	1815	1590	1357	603	33
Testosterone	2596	2512	2351	2137	1846	1621	1395	659	40

F Nonfatal Stroke: Safety Population



No. at Risk									
Placebo	2602	2525	2347	2111	1819	1600	1366	610	34
Testosterone	2596	2520	2362	2149	1856	1629	1405	665	39

discontinued placebo (Fig. S2); patients received the assigned regimen for 67.5% and 67.3% of the potential treatment time in the testosterone and placebo groups, respectively. A total of 1082 patients (20.8%) withdrew from the trial before end-of-trial visits began, and an additional 947 patients (18.2%) did not attend their end-of-trial visit after that date. Withdrawal rates were similar in the two trial groups, and outcome data were available for 82.7% of the possible follow-

Figure 2 (facing page). Time-to-Event Analysis for the Primary and Secondary Cardiovascular Safety End Points.

Panel A shows the cumulative incidence of the primary cardiovascular composite safety end point, which was defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Panel B shows the cumulative incidence of the primary cardiovascular composite safety end point in the primary sensitivity analysis population in which data on endpoint events that occurred more than 365 days after discontinuation of testosterone or placebo were censored. Panel C shows the cumulative incidence of the secondary cardiovascular composite safety end point of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization; Panel D, the cumulative incidence of death due to cardiovascular causes; Panel E, the cumulative incidence of nonfatal myocardial infarction; and Panel F, the cumulative incidence of nonfatal stroke. The definitions of all end points are provided in the Supplementary Appendix. In each case, the cumulative incidence was estimated with the Kaplan–Meier method, and the hazard ratio was calculated with the Cox proportional-hazards regression model with adjustment for preexisting cardiovascular disease (yes or no) as a covariate. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other end points, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary end points. The insets show the same data on an enlarged y axis.

up time (observed person-time divided by total person-time, on the assumption of no withdrawals)[13] in the testosterone group and 81.7% of the possible follow-up time in the placebo group.

TRIAL END POINTS

The mean (±SD) daily dose of testosterone was 65±22 mg. Serum testosterone levels that were measured approximately 24 hours after the patient had received a dose of testosterone or placebo over the course of the trial are shown in Figure 1 and Table S3. At 12 months, the median increase from baseline in serum testosterone levels was 148 ng per deciliter; interquartile range, 34 to 312 (5.1 nmol per liter; interquartile range, 1.2 to 10.8) in the testosterone group, as compared with a median increase of 14 ng per deciliter; interquartile range, –21 to 56 (0.5 nmol per liter; interquartile range, –0.7 to 1.9) in the placebo group. Estradiol levels are summarized in Table S4.

A primary safety end-point event (the first adjudicated major adverse cardiac event) occurred in 182 patients (7.0%) in the testosterone group and in 190 patients (7.3%) in the placebo group (hazard ratio, 0.96; 95% confidence interval [CI], 0.78 to 1.17; P<0.001 for noninferiority) (Fig. 2A and Table 2). In the principal sensitivity analysis (with censoring of data on events that occurred >365 days after the last dose), a primary safety end-point event occurred in 154 patients (5.9%) in the testosterone group and in 152 patients (5.8%) in the placebo group (hazard ratio, 1.02; 95% CI, 0.81 to 1.27; P<0.001 for noninferiority) (Fig. 2B). Similar findings were observed in sensitivity analyses in which data on events were censored more than 30 days after the last dose or after interruption of testosterone or placebo, in the confirmatory analysis involving the full-analysis population, and among prespecified subgroups; analysis of the restricted mean survival time at 3 years met the criteria for noninferiority (Figs. S3 and S4 and Table S5).

No apparent clinically meaningful differences in the incidence of secondary cardiovascular end-point events were observed between the trial groups (Table 2 and Fig. 2C through 2F). A higher incidence of pulmonary embolism, a component of the adjudicated tertiary end point of venous thromboembolic events (Table 2), occurred in the testosterone group than in the placebo group (0.9% vs. 0.5%).

ADVERSE EVENTS

Prostate cancer occurred in 12 patients (0.5%) in the testosterone group and in 11 patients (0.4%) in the placebo group (P=0.87); these cases were adjudicated as high-grade prostate cancer (Gleason score, 4+3 or higher, indicating an intermediate or higher risk of progression) in 5 patients and 3 patients, respectively (P=0.51). The increase in PSA levels from baseline was greater in patients in the testosterone group than in those in the placebo group (0.20±0.61 ng per milliliter vs. 0.08±0.90 ng per milliliter, respectively; P<0.001). The change in mean systolic blood pressure from baseline through 6 months was 0.3 mm Hg (95% CI, –0.3 to 0.9) in the testosterone group and –1.5 mm Hg (95% CI, –2.0 to –0.9) in the placebo group (P<0.001) (Table S6). Investigator-reported adverse events are summarized in Table 3. Nonfatal arrhythmias warranting intervention occurred in 134 patients (5.2%) in the testosterone group and in 87 patients (3.3%) in the placebo group (P=0.001); atrial fibrillation

Table 2. Adjudicated Cardiovascular End Points in the Safety Population.*

End Point	Testosterone Group (N=2596)	Placebo Group (N=2602)	Hazard Ratio (95% CI)†
	number of patients (percent)		
Primary cardiovascular composite end point: major adverse cardiac events‡	182 (7.0)	190 (7.3)	0.96 (0.78–1.17)
Secondary cardiovascular composite end point§	269 (10.4)	264 (10.1)	1.02 (0.86–1.21)
Components of primary and secondary composite end points			
Death from cardiovascular causes	87 (3.4)	103 (4.0)	0.84 (0.63–1.12)
Nonfatal myocardial infarction	68 (2.6)	62 (2.4)	1.10 (0.78–1.56)
Nonfatal stroke	36 (1.4)	38 (1.5)	0.94 (0.60–1.49)
Coronary revascularization	144 (5.5)	121 (4.6)	1.20 (0.95–1.53)
Tertiary end points			
Death from any cause	144 (5.5)	148 (5.7)	0.98 (0.78–1.23)
Hospitalization or urgent visit for heart failure	55 (2.1)	50 (1.9)	1.11 (0.76–1.62)
Peripheral arterial revascularization	30 (1.2)	33 (1.3)	0.92 (0.56–1.51)
Venous thromboembolic events¶	44 (1.7)	30 (1.2)	1.46 (0.92–2.32)
Components of venous thromboembolic events‖			
Pulmonary embolism	24 (0.9)	12 (0.5)	—
Deep venous thrombosis	16 (0.6)	13 (0.5)	—
Other peripheral venous thrombosis	11 (0.4)	12 (0.5)	—

* The safety population consisted of all patients who had undergone randomization and received at least one dose of testosterone or placebo.

† The analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other end points, so results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary end points.

‡ The composite end point of major adverse cardiac events in the primary analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. P<0.001 for the noninferiority of testosterone to placebo with regard to this end point.

§ The secondary composite cardiovascular end point was the first occurrence of the components of the primary end point (major adverse cardiac events) plus coronary revascularization procedures (percutaneous coronary intervention or coronary-artery bypass graft surgery).

¶ Venous thromboembolic events include pulmonary embolism, deep venous thrombosis, and other peripheral venous thrombosis. Other peripheral venous thrombosis must have been confirmed by imaging and included thrombosis in the calf, portal, subclavian, or mesenteric veins. Superficial thrombophlebitis alone was not considered a venous thromboembolic event.

‖ There was no prespecified plan to calculate hazard ratios for the individual components of venous thromboembolic events.

occurred in 91 patients (3.5%) and 63 patients (2.4%), respectively (P=0.02), and acute kidney injury occurred in 60 patients (2.3%) and 40 patients (1.5%), respectively (P=0.04).

DISCUSSION

We conducted this randomized, placebo-controlled trial to address uncertainty as to whether testosterone-replacement therapy in middle-aged and older men with hypogonadism increases the risk of cardiovascular events. We included men with established cardiovascular disease or multiple cardiac risk factors who would be most vulnerable to an increased risk of adverse cardiovascular outcomes. Among 5198 patients who received testosterone or placebo for a mean duration of 22 months, testosterone-replacement therapy was noninferior to placebo with respect to the incidence of major adverse cardiac events. The hazard ratio for a primary end-point event was 0.96 (95% CI, 0.78 to 1.17), a noninferiority finding

Table 3. Investigator-Reported Adverse Events.*

Event	Testosterone Group (N=2596)	Placebo Group (N=2602)	P Value†
	number of patients (percent)		
Any adverse event	1187 (45.7)	1164 (44.7)	0.47
Serious adverse event	721 (27.8)	697 (26.8)	0.42
Adverse event leading to discontinuation of testosterone or placebo	244 (9.4)	226 (8.7)	0.37
Prespecified adverse events of special interest	196 (7.6)	167 (6.4)	0.11
Hospitalization for unstable angina	44 (1.7)	60 (2.3)	0.12
Nonfatal arrhythmia warranting intervention	134 (5.2)	87 (3.3)	0.001
Cardiovascular disease causing syncope	27 (1.0)	32 (1.2)	0.52
Transient ischemic attack	15 (0.6)	17 (0.7)	0.73
Other adverse events			
Diabetes mellitus	189 (7.3)	213 (8.2)	0.22
Coronavirus disease 2019	121 (4.7)	117 (4.5)	0.78
Atrial fibrillation	91 (3.5)	63 (2.4)	0.02
Pneumonia	64 (2.5)	56 (2.2)	0.45
Acute kidney injury	60 (2.3)	40 (1.5)	0.04
Benign prostatic hyperplasia	45 (1.7)	46 (1.8)	0.92
Acute respiratory failure	52 (2.0)	37 (1.4)	0.11
Urinary retention	50 (1.9)	34 (1.3)	0.08
Cellulitis	35 (1.3)	46 (1.8)	0.22
Congestive cardiac failure	34 (1.3)	41 (1.6)	0.42

* The safety population consisted of all patients who had undergone randomization and received at least one dose of testosterone or placebo. Events are classified according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 25.0.
† P values were calculated with the use of a chi-square test.

that was confirmed in sensitivity analyses with adjustment for the influence of interruptions or discontinuations of testosterone or placebo.

The FDA initiated a review of the cardiovascular safety of testosterone products in 2010 after a small placebo-controlled trial was prematurely discontinued because of an increased incidence of cardiovascular events among patients who received testosterone therapy.[14] However, subsequent meta-analyses showed variable results and most, including a recent patient-level meta-analysis,[15] did not confirm these findings. Cardiac events in those trials were not uniformly adjudicated, definitions were broad and inconsistent, and the trials were not adequately powered for cardiovascular outcomes. Retrospective observational studies, which were limited by potential confounding and selection bias, also showed conflicting findings,[1-5] although one analysis from a large health care database suggested that an age of 65 years or older or preexisting cardiovascular disease might be important modifiers of increased risk with testosterone-replacement therapy.[2] Nearly half the patients enrolled in the current trial were 65 years of age or older, and more than half had preexisting cardiovascular disease. The 372 adjudicated primary end-point events that occurred in this trial were greater in number than those in all previous randomized trials of testosterone combined.

The incidence of pulmonary embolism was higher with testosterone than with placebo. Although most reported cases of thrombosis associated with testosterone therapy have been in men with underlying thrombophilia,[16] a meta-analysis of randomized trials did not show an association between venous thromboembolic events and testosterone use in wider populations.[15] Our findings support current guidelines that testosterone should be used with caution in men

who have had previous thromboembolic events.[17] There were more cases of nonfatal arrhythmias warranting intervention, atrial fibrillation, and acute kidney injury among patients who received testosterone than among those who received placebo; these adverse events were not expected. A cohort study suggested that normalization of low testosterone levels by testosterone-replacement therapy was associated with a decrease in the incidence of atrial fibrillation.[18] In the current trial, the small increase in blood pressure observed in the testosterone group was similar to that reported previously with other testosterone formulations.[19]

Our trial design specified that noninferiority testing for cardiovascular safety be performed in the population of all patients who had undergone randomization and who had received at least one dose of testosterone or placebo. This modified intention-to-treat analysis preserves the integrity of randomization but may attenuate differences between trial groups and bias toward noninferiority when patients are not adherent to or discontinue their assigned testosterone or placebo. We therefore planned three on-treatment sensitivity analyses and specified that the trial would not conclude until accrual of at least 256 primary end-point events that met the criteria for the principal sensitivity analysis. By considering only those end-point events that occurred while patients were receiving testosterone or placebo or within a time frame of physiologic effect after discontinuation of testosterone or placebo, on-treatment analyses can strengthen safety signals by providing more specific accounting of outcomes related to testosterone therapy. These sensitivity analyses provided support for the noninferiority conclusions.

The incidence of adherence and of retention was lower in this trial than in most cardiovascular outcome studies. Similar levels of adherence and retention have been reported in other trials of testosterone[20,21] as well as other therapies for symptomatic conditions such as menopause,[22,23] obesity,[24,25] and chronic pain.[26] These findings reflect the challenge of retaining patients who have persistent symptoms and choose to switch medications or discontinue trial participation. The consistency of the results derived from the intention-to-treat and on-treatment sensitivity analyses suggests that the noninferiority conclusions were unlikely to have been influenced by nonadherence. The effect of nonretention, however, is more difficult to quantify, and the possibility of bias due to informative censoring cannot be ruled out despite a similar incidence of nonretention in the two trial groups. It is somewhat reassuring that of the patients who discontinued trial participation, nearly half did so after end-of-trial visits began, and outcome data were available for more than 80% of the potential person-time follow-up.

Controlled trials have shown that the use of testosterone in older men improves sexual function,[27-29] increases volumetric and areal bone mineral density,[30] corrects unexplained anemia,[31,32] and moderately reduces depressive symptoms.[33] However, because testosterone deficiency is not a life-threatening condition, uncertainty about cardiovascular outcomes has weighed on treatment decisions by clinicians and patients.[17] Our findings regarding the cardiovascular safety of testosterone may facilitate a more informed consideration of the potential benefits and risks of testosterone therapy among middle-aged and older men with hypogonadism.

Among men with hypogonadism and established cardiovascular disease or multiple risk factors for incident cardiac events, testosterone-replacement therapy was noninferior to placebo with respect to the occurrence of major adverse cardiac events during a mean 22-month follow-up, and the overall incidence of adverse events was low.

Supported by AbbVie, Acerus Pharmaceuticals, Endo Pharmaceuticals, and Upsher–Smith Laboratories.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: A. Michael Lincoff, M.D., Shalender Bhasin, M.B., B.S., Panagiotis Flevaris, M.D., Ph.D., Lisa M. Mitchell, R.N., B.S.N., Shehzad Basaria, M.D., William E. Boden, M.D., Glenn R. Cunningham, M.D., Christopher B. Granger, M.D., Mohit Khera, M.D., M.P.H., Ian M. Thompson, Jr., M.D., Qiuqing Wang, M.S., Kathy Wolski, M.P.H., Deborah Davey, R.N., Vidyasagar Kalahasti, M.D., Nader Khan, M.D., Michael G. Miller, Pharm.D., Michael C. Snabes, M.D., Ph.D., Anna Chan, Pharm.D., Elena Dubcenco, M.D., Xue Li, Ph.D., Tingting Yi, Ph.D., Bidan Huang, Ph.D., Karol M. Pencina, Ph.D., Thomas G. Travison, Ph.D., and Steven E. Nissen, M.D.

The authors' affiliations are as follows: the Cleveland Clinic Coordinating Center for Clinical Research, Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland (A.M.L., L.M.M., Q.W., K.W., D.D., V.K., S.E.N.); the Research Program in Men's Health: Aging

and Metabolism, Brigham and Women's Hospital, Harvard Medical School (S. Bhasin, S. Basaria, K.M.P.), Veterans Affairs Boston Healthcare System and Massachusetts Veterans Epidemiology, Research, and Information Center, Boston University School of Medicine (W.E.B.), and Marcus Institute for Aging Research, Beth Israel Deaconess Medical Center, Harvard Medical School (T.G.T.) — all in Boston; AbbVie, North Chicago, IL (P.F., N.K., M.G.M., M.C.S., A.C., E.D., X.L., T.Y., B.H.); Baylor College of Medicine, Houston (G.R.C., M.K.), and CHRISTUS Santa Rosa Health System and the University of Texas Health Science Center, San Antonio (I.M.T.) — all in Texas; and Duke Clinical Research Institute, Durham, NC (C.B.G.).

REFERENCES

1. Baillargeon J, Urban RJ, Kuo Y-F, et al. Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother 2014;48:1138-44.
2. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014;9(1):e85805.
3. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013;169:725-33.
4. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012;97:2050-8.
5. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829-36.
6. Alexander GC, Iyer G, Lucas E, Lin D, Singh S. Cardiovascular risks of exogenous testosterone use among men: a systematic review and meta-analysis. Am J Med 2017; 130:293-305.
7. Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf 2014;13:1327-51.
8. Elliott J, Kelly SE, Millar AC, et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis. BMJ Open 2017;7(11):e015284.
9. Onasanya O, Iyer G, Lucas E, Lin D, Singh S, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. Lancet Diabetes Endocrinol 2016; 4:943-56.
10. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med 2013; 11:108.
11. Food and Drug Administration. FDA cautions about using testosterone products for low testosterone due to aging: requires labeling change to inform of possible increased risk of heart attack and stroke with use. FDA drug safety communication. 2018 (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-cautions-about-using-testosterone-products-low-testosterone-due).
12. Bhasin S, Lincoff AM, Basaria S, et al. Effects of long-term testosterone treatment on cardiovascular outcomes in men with hypogonadism: rationale and design of the TRAVERSE study. Am Heart J 2022; 245:41-50.
13. Xue X, Agalliu I, Kim MY, et al. New methods for estimating follow-up rates in cohort studies. BMC Med Res Methodol 2017;17:155.
14. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109-22.
15. Hudson J, Cruickshank M, Quinton R, et al. Adverse cardiovascular events and mortality in men during testosterone treatment: an individual patient and aggregate data meta-analysis. Lancet Healthy Longev 2022;3(6):e381-e393.
16. Glueck CJ, Wang P. Testosterone therapy, thrombosis, thrombophilia, cardiovascular events. Metabolism 2014;63:989-94.
17. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2018;103:1715-44.
18. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone levels after testosterone replacement therapy is associated with decreased incidence of atrial fibrillation. J Am Heart Assoc 2017;6(5): e004880.
19. White WB, Bernstein JS, Rittmaster R, Dhingra O. Effects of the oral testosterone undecanoate Kyzatrex on ambulatory blood pressure in hypogonadal men. J Clin Hypertens 2021;23:1420-30.
20. Basaria S, Harman SM, Travison TG, et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: a randomized clinical trial. JAMA 2015;314: 570-81.
21. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005;90:1502-10.
22. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002;288:49-57.
23. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
24. Bohula EA, Wiviott SD, McGuire DK, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. N Engl J Med 2018;379:1107-17.
25. Nissen SE, Wolski KE, Prcela L, et al. Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. JAMA 2016;315:990-1004.
26. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2016;375:2519-29.
27. Brock G, Heiselman D, Maggi M, et al. Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo controlled study. J Urol 2016;195: 699-705.
28. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Testosterone treatment and sexual function in older men with low testosterone levels. J Clin Endocrinol Metab 2016;101:3096-104.
29. Steidle C, Schwartz S, Jacoby K, et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab 2003;88:2673-81.
30. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, et al. Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. JAMA Intern Med 2017;177:471-9.
31. Bachman E, Travison TG, Basaria S, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. J Gerontol A Biol Sci Med Sci 2014;69:725-35.
32. Roy CN, Snyder PJ, Stephens-Shields AJ, et al. Association of testosterone levels with anemia in older men: a controlled clinical trial. JAMA Intern Med 2017;177: 480-90.
33. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. N Engl J Med 2016;374:611-24.