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Testosterone Treatment and Fractures in Men with Hypogonadism

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- **Testosterone treatment** in men who have hypogonadism due to pituitary or testicular disease has been reported to improve many measures of their bone structure and quality. Studies have shown that such testosterone treatment increased areal bone density on dualenergy x-ray absorptiometry1-3 and volumetric bone density on quantitative computed tomography (CT).

In addition, testosterone treatment improved many measures of bone structure and quality in men with moderate hypogonadism associated with aging.

Testosterone treatment in these men for 3 years increased areal bone mineral density of the spine.

In the Bone Trial within the Testosterone Trials, testosterone treatment for 1 year in older men with hypogonadism increased volumetric bone mineral density and estimated strength of the spine and hip on quantitative CT.

Severe hypogonadism has been associated with an increased risk of clinical fractures among men with prostate cancer. Men with prostate cancer in whom severe hypogonadism develops after treatment with “superactive” agonists of gonadotropin-releasing hormone have been observed to be more likely to sustain a fracture than men with prostate cancer who have not received this treatment.

Trials with a sufficiently large sample and a sufficiently long duration to determine the effect of testosterone therapy on the incidence of fractures are needed to determine whether such treatment would reduce the risk of fracture. The present subtrial of the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial, which was a phase 4 trial designed primarily to determine whether testosterone treatment in middle-aged and older men with hypogonadism would increase the incidence of major adverse cardiovascular events,offered the opportunity to determine whether testosterone treatment would reduce the risk of clinical fractures.

Methods

The present Fracture Trial was a subtrial of the double-blind, randomized, placebo-controlled TRAVERSE trial. This planned subtrial assessed the effect of testosterone treatment on the incidence of clinical fractures among all the participants in the TRAVERSE trial. The parent trial was conducted at 316 sites in the United States and was funded by a consortium of manufactur ers of testosterone, led by AbbVie.

Participants were recruited from community clinical practices. Entry criteria included male sex, an age of 45 to 80 years, and clinical hypogonadism, defined by two morning testosterone concentrations of less than 300 ng per deciliter (10.4 nmol per liter), in fasting plasma samples obtained at least 48 hours apart, and one or more symptoms of hypogonadism.

Participants were also required to have evidence of preexisting cardiovascular disease or an increased risk of cardiovascular disease. Osteoporosis was not a criterion for entry. Among the exclusion criteria were a serum testosterone concentration of less than 100 ng per deciliter (3.5 nmol per liter) and conditions that might be worsened by testosterone treatment, such as prostate cancer, sever lower urinary tract symptoms, a hematocrit of more than 50%, and severe untreated sleep apnea.

Participants were randomly assigned in a 1:1 ratio to receive either a transdermal 1.62% testosterone gel or matching placebo gel. Randomization was stratified according to the presence or absence of preexisting cardiovascular disease. The testosterone gel was supplied in a pump bottle; each depression yielded 20.25 mg of testosterone. Participants applied the gel once per day, initially one depression of the pump bottle to each shoulder.

The dose was adjusted, with the use of a prespecified algorithm, to attempt to maintain a serum testosterone concentration of 350 to 750 ng per deciliter (12.1 to 26.0 nmol per liter) and a hematocrit of less than 54%. The serum testosterone concentration was measured at weeks 2, 4, 12, 26, 52, 78, and 104 and then yearly. The dose was adjusted in participants in the placebo group to maintain blinding. Testosterone or placebo was discontinued if the serum testosterone concentration remained more than 750 ng per deciliter or the hematocrit remained more than 54% at the lowest daily dose of testosterone (20.25 mg) or if prostate cancer developed.

Participants were asked at each in-person or telephone visit if they had had a fracture since their previous visit. If they had, they were asked about the nature of the injury and the location of the fracture or fractures; they were also asked for permission to obtain source documents, including radiology reports.

Records of reported fractures were reviewed by an adjudicator at the San Francisco Coordinating Center who was unaware of the trialgroup assignments; the adjudicator classified the reported fracture as follows: confirmed fracture, confirmed not to be a fracture, fracture uncertain, or insufficient documentation to determine. When documentation was insufficient, an attempt was made to obtain additional documentation, including radiographs.

Fracture End Points

The main fracture end point, which was assessed in a time-to-event analysis, was the first clinical fracture, defined as a clinical spine or non-spine fracture that was documented by imaging or surgery and confirmed by adjudication. Fractures of the sternum, fingers, toes, facial bones, and skull were excluded. Other prespecified end points were time to first non–high-impact clinical fracture; time to first clinical fracture in participants not taking a medication to treat osteoporosis; time to first non–high-impact clinical fracture in participants not taking a medication to treat osteoporosis;

time to first clinical fracture not excluding fractures of the sternum, fingers, toes, facial bones, and skull; time to first clinical fracture not excluding those classified as uncertain; time to any major osteoporotic fracture (hip, humerus, wrist, and clinical spine); time to hip fracture; and time to clinical vertebral fracture.

Statistical Analysis

The parent trial was designed to continue until at least 256 major adverse cardiovascular events had occurred, which was estimated to require enrollment of up to 6000 men for a mean of 3 years.Before enrollment, we estimated the power of the trial to detect a clinically significant decrease in fracture risk.

analyses of serum testosterone, dihydrotestosterone, and estradiol concentrations were conducted in the safety population of participants who had undergone randomization and received at least one dose of testosterone or placebo; measurements only within 30 days after the last dose of testosterone or placebo were analyzed.

Results

Enrollment was conducted from May 23, 2018, to February 1, 2022. The last participant completed trial assessments on January 19, 2023. the full-analysis population included 5204 participants: 2601 in the testosterone group and 2603 in the placebo group. The safety population included 5198 participants who had received at least one dose: 2596 in the testosterone group and 2602 in the placebo group.

The two trial groups were similar with respect to age, race, serum testosterone and estradiol concentrations, and the use of medications to treat osteoporosis.

Of the participants who were enrolled (safety population), 4804 (92.4%) were followed for at least 1 year, 3842 (73.9%) for at least 2 years, and 2974 (57.2%) for at least 3 years. The median duration of participation was 3.19 years (interquartile range, 1.96 to 3.53).

Adherence, determined by comparison of the weights of the pump bottles when dispensed and when returned, was approximately 90% in both trial groups. The incidence of early discontinuation of testosterone or placebo while continuing trial assessments (61.6%) and early withdrawal from the trial and having no further assessments (39.0%) was relatively high but was similar in the two trial groups

The median serum testosterone concentration in the testosterone group increased at month 6 and remained higher than baseline through year 3, The median serum testosterone concentration did not change substantially among the participants assigned to receive placebo.

The emedian serum concentrations of dihydrotestosterone and estradiol also increased among the participants assigned to receive testosterone but not among those assigned to receive placebo.

During the trial, 309 fractures in 224 participants were reported, including 186 fractures in the testosterone group and 123 in the placebo group (Table 1).

Of these, 154 in the testosterone group and 97 in the placebo group were confirmed to be fractures, and 8 in the testosterone group and 6 in the placebo group were confirmed not to be fractures.

The remaining 44 reported fractures could not be confirmed to be fractures or not because of insufficient documentation or uncertainty after review of available medical records.

Table 1. Outcomes of Adjudication of Reported Fractures.*

Adjudication Outcome	Testosterone	Placebo
Total fractures reported and adjudicated — no.	186	123
Confirmed fracture — no. (%)	154 (82.8)	97 (78.9)
Confirmed not to be a fracture — no. (%)	8 (4.3)	6 (4.9)
Unconfirmed — no. (%)	24 (12.9)	20 (16.3)
Fracture uncertain	9 (4.8)	7 (5.7)
Insufficient documentation	15 (8.1)	13 (10.6)

* Medical records of reported fractures were evaluated by a trained adjudicator, who judged the evidence as confirming that a fracture had occurred, confirming that a fracture had not occurred, or not confirming either way (unconfirmed) owing to insufficient documentation or lack of clarity of the documentation (fracture uncertain).

A total of 91 of 2601 participants (3.50%) in the testosterone group and 64 of 2603 participants (2.46%) in the placebo group had one or more clinical fractures, excluding fractures of the sternum, fingers, toes, facial bones, and skull (hazard ratio, 1.43; 95% confidence interval [CI], 1.04 to 1.97)

Subgroup	Testosterone	Placebo	Hazard Ratio for Fracture (95% CI)
	no. with fracture/no. at risk (%)		
All clinical fractures	91/2601 (3.50)	64/2603 (2.46)	1.43 (1.04–1.97)
Non–high-impact clinical fractures	75/2601 (2.88)	57/2603 (2.19)	1.32 (0.94–1.86)
Clinical fractures in participants not taking osteoporosis medication	88/2588 (3.40)	63/2592 (2.43)	1.41 (1.02–1.94)
Non–high-impact fractures in participants not taking osteoporosis medication	72/2588 (2.78)	56/2592 (2.16)	1.29 (0.91–1.83)
Fracture-free survival	226/2601 (8.69)	198/2603 (7.61)	1.15 (0.95–1.39)
All clinical fractures, including those that had been excluded	109/2601 (4.19)	72/2603 (2.77)	1.52 (1.13–2.05)
All clinical fractures including uncertain and insufficient documentation	99/2601 (3.81)	75/2603 (2.88)	1.33 (0.98–1.79)
Major osteoporotic fractures: hip, wrist, humerus, and clinical spine	36/2601 (1.38)	30/2603 (1.15)	1.20 (0.74–1.95)
Hip fractures	7/2601 (0.27)	6/2603 (0.23)	1.16 (0.39–3.46)
Clinical vertebral fractures	14/2601 (0.54)	11/2603 (0.42)	1.26 (0.57–2.79)

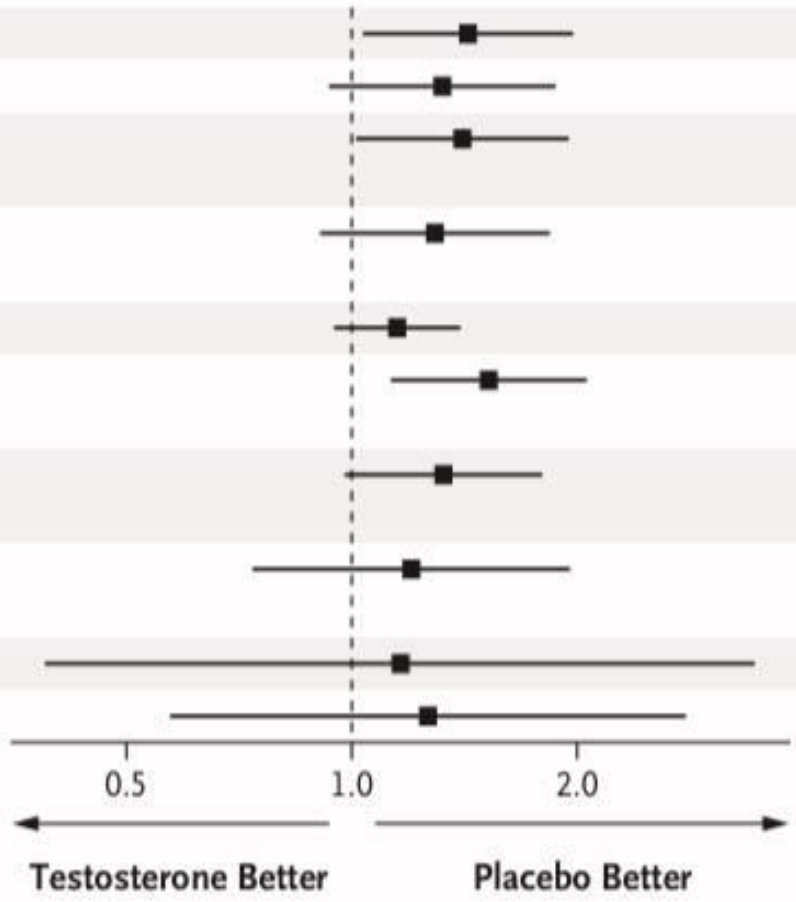
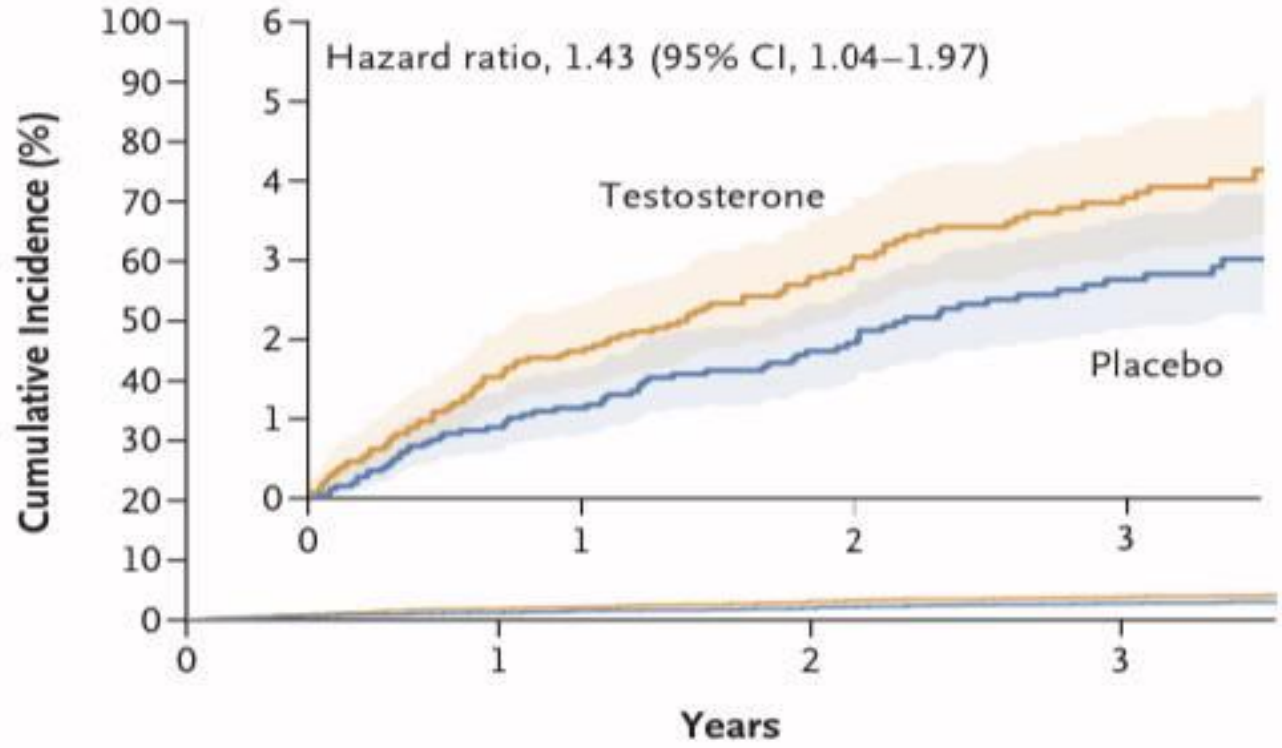


Figure 1. Fracture End Points.

The forest plot on the right shows that participants who received testosterone had a numerically higher incidence of all types of fractures than those who received placebo. Data for "all clinical fractures" include all the participants who had one or more clinical fractures, excluding fractures of the sternum, fingers, toes, facial bones, and skull. Confidence intervals are unadjusted for multiple comparisons and are not a substitute for hypothesis tests.

The cumulative incidence of clinical fracture at year 3 was 3.8% (95% CI, 3.0 to 4.6) in the testosterone group and 2.8% (95% CI, 2.1 to 3.5%) in the placebo group .



No. at Risk				
Testosterone	2601	2332	1812	1369
Placebo	2603	2335	1812	1354

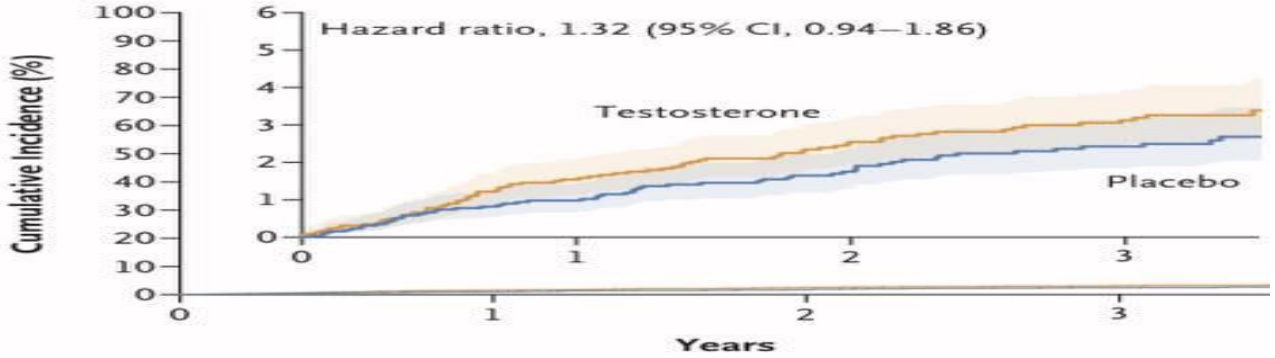
Figure 2. Cumulative Incidence of All Clinical Fractures.

Fractures of the sternum, fingers, toes, facial bones, and skull were excluded from the analysis. The inset shows the same data on an expanded y axis. Pointwise 95% confidence interval bands are shown, as is the cause-specific hazard ratio with unadjusted 95% confidence interval. Confidence intervals are unadjusted for multiple comparisons and are not a substitute for hypothesis tests.

Testosterone was also associated with a higher fracture incidence than placebo for other fracture end points. The forest plot in Figure 1 shows the consistency of the association of testosterone treatment with a higher incidence of fractures of all types.

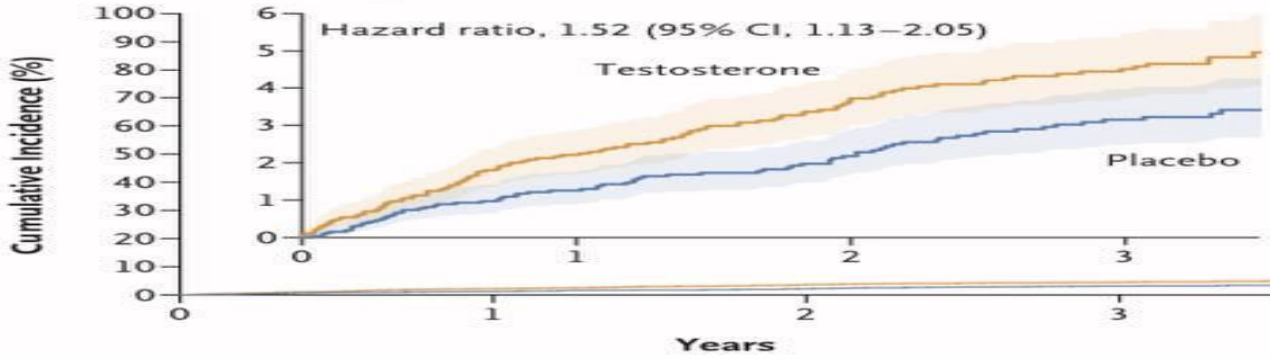
The cumulative incidence in the two trial groups of non–high-impact fractures, all clinical fractures (including those that had been excluded from the primary analysis), and clinical fractures in participants not taking medication for osteoporosis is shown in Figure 3.

A Non–High-Impact Clinical Fractures



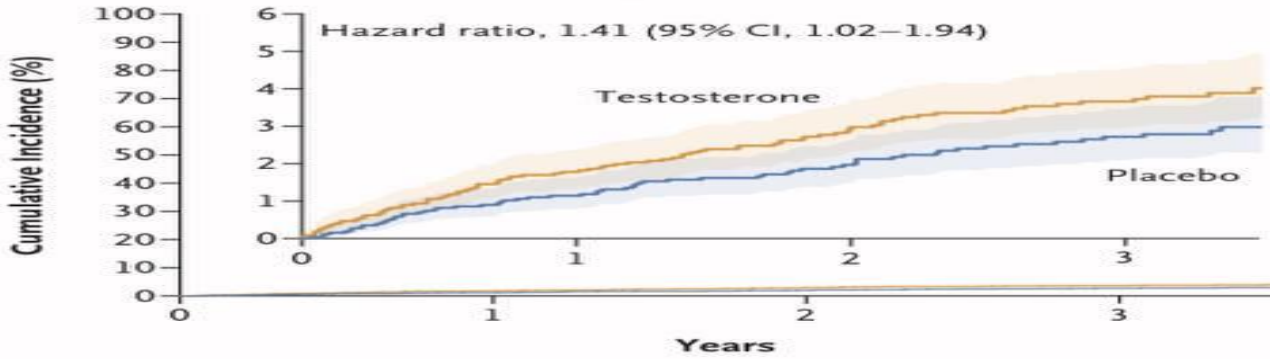
No. at Risk				
Testosterone	2601	2339	1822	1375
Placebo	2603	2337	1815	1357

B All Clinical Fractures, Including Those That Had Been Excluded



No. at Risk				
Testosterone	2601	2324	1799	1355
Placebo	2603	2332	1807	1348

C Clinical Fractures in Participants Not Taking Osteoporosis Medication



No. at Risk				
Testosterone	2588	2323	1805	1364
Placebo	2592	2324	1805	1350

Most fractures in both trial groups were associated with trauma, more commonly with falls (Table 2). The most common sites of fractures were ribs, wrist, and ankle. Traumatic events and falls were not prespecified end points, but clinically significant trauma was captured by the reporting of serious adverse events.

Serious adverse events involving the musculoskeletal system were reported in 66 participants (2.5%) in the testosterone group and 65 participants (2.5%) in the placebo group.

Table 2. Fractures and Trauma.*

Fracture Type	Testosterone (N=2601)	Placebo (N=2603)
	no. of participants (%)	
Any confirmed fracture	109 (4.19)	72 (2.77)
Fracture that was excluded from analysis of all clinical fractures†	27 (1.04)	13 (0.50)
Fracture that was included in analysis of all clinical fractures	91 (3.50)	64 (2.46)
Fracture associated with trauma	84 (3.23)	58 (2.23)
Fall	58 (2.23)	43 (1.65)
From standing height or less	43 (1.65)	35 (1.34)
From more than standing height	8 (0.31)	5 (0.19)
On stairs or curb	7 (0.27)	4 (0.15)
Non-fall	25 (0.96)	15 (0.58)
Minimal to moderate	9 (0.35)	7 (0.27)
Severe	16 (0.62)	8 (0.31)
Undetermined type of trauma	2 (0.08)	2 (0.08)
Fracture not associated with trauma	6 (0.23)	6 (0.23)
Spontaneous	1 (0.04)	0
Stress	2 (0.08)	1 (0.04)
Pathologic	3 (0.12)	5 (0.19)
Fracture with undetermined association with trauma	3 (0.12)	0

* Shown are the numbers of participants with at least one fracture of the stated type.
† Excluded were fractures of the sternum, fingers, toes, facial bones, and skull.

Discussion

In this subtrial involving middle-aged and older men with hypogonadism, the 3-year cumulative **incidence of all clinical fractures was 3.8% in the testosterone group and 2.8% in the placebo group.**

The fracture incidence was also numerically **higher in the testosterone group for all other fracture end points.**

The end point of all clinical fractures is the same as that used in several trials of treatments for osteoporosis.

The most common anatomical sites of fractures were ribs, wrist, and ankle, findings similar to those in previous studies involving men.

These sites are of clinical **significance** because fractures at these sites are associated with **low bone mineral density** and with previous fractures,and are therefore considered **osteoporotic fractures**.

More important, they are associated with an increased risk of future fractures and increased mortality.

We did not expect these results, because most previous studies showed that testosterone improved many measures of bone structure and quality.

In studies involving men with severe hypogonadism, testosterone treatment increased areal and volumetric bone mineral density1-4 and improved many structural and mechanical measures of trabecular bone on magnetic resonance microimaging.

one study showed that testosterone treatment in men with severe hypogonadism decreased cortical bone volume fraction and cortical bone axial thickness,a measure of bone strength.

The fact that testosterone was associated with increased fracture risk among middle-aged and older men with hypogonadism should be considered in the context of potential benefits and other risks of testosterone treatment in these men.

The Testosterone Trials showed that testosterone treatment improved sexual function and mood and increased hemoglobin levels in older men.

In the present trial, testosterone was not associated with an increased risk of major adverse cardiovascular events but was associated with increased risks of atrial fibrillation, pulmonary embolism, and acute kidney injury.

We found that among middle-aged and older men with hypogonadism, testosterone treatment did not result in a lower incidence of clinical fracture than placebo.

The fracture incidence was numerically higher among men who received testosterone than among those who received placebo.


با تشکر از توجه شما