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Testosterone Treatment and Fractures in Men with Hypogonadism

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ABSTRACT

BACKGROUND

Testosterone treatment in men with hypogonadism improves bone density and quality, but trials with a sufficiently large sample and a sufficiently long duration to determine the effect of testosterone on the incidence of fractures are needed.

METHODS

In a subtrial of a double-blind, randomized, placebo-controlled trial that assessed the cardiovascular safety of testosterone treatment in middle-aged and older men with hypogonadism, we examined the risk of clinical fracture in a time-to-event analysis. Eligible men were 45 to 80 years of age with preexisting, or high risk of, cardiovascular disease; one or more symptoms of hypogonadism; and 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. Participants were randomly assigned to apply a testosterone or placebo gel daily. At every visit, participants were asked if they had had a fracture since the previous visit. If they had, medical records were obtained and adjudicated.

RESULTS

The full-analysis population included 5204 participants (2601 in the testosterone group and 2603 in the placebo group). After a median follow-up of 3.19 years, a clinical fracture had occurred in 91 participants (3.50%) in the testosterone group and 64 participants (2.46%) in the placebo group (hazard ratio, 1.43; 95% confidence interval, 1.04 to 1.97). The fracture incidence also appeared to be higher in the testosterone group for all other fracture end points.

CONCLUSIONS

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. (Funded by AbbVie and others; TRAVERSE ClinicalTrials.gov number, NCT03518034.)

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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 dual-energy x-ray absorptiometry[1-3] and volumetric bone density on quantitative computed tomography (CT).[1,4] Testosterone treatment also improved many topological measures of trabecular architecture on magnetic resonance microimaging.[5-7]

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.[8,9] 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.[10]

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.[11-13]

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,[14] offered the opportunity to determine whether testosterone treatment would reduce the risk of clinical fractures.

Methods

Trial Design and Oversight

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 manufacturers of testosterone, led by AbbVie. The parent trial was overseen by the Cleveland Clinic Coordinating Center for Clinical Research and supported logistically by Labcorp Drug Development. The protocol for the parent trial, which is available with the full text of this article at NEJM.org, was designed by an executive committee and AbbVie. The protocol for the Fracture Trial was designed by a separate fracture committee (members are listed in the Supplementary Appendix, available at NEJM.org). The protocol was approved by the institutional review board at each participating institution. A data monitoring committee also approved the protocol and monitored unblinded interim data. Labcorp Drug Development maintained the clinical database and transferred the data to the University of Wisconsin Statistical Data Analysis Center for statistical analysis related to fractures.

The overall trial design has been described,[14] and the results of the cardiovascular outcomes have been reported.[15] The first author wrote the first draft of the manuscript, and all the authors contributed to subsequent drafts. Representatives of AbbVie also suggested revisions. The fracture committee made final decisions about content. The first and fifth authors vouch for the completeness and accuracy of the data and for the fidelity of the analyses to the statistical analysis plan, available with the protocol. All the trial participants provided written informed consent.

Participants

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, severe

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,[14,15] 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.

ASSESSMENTS

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 trial-group assignments; the adjudicator was trained by the second author, who also reviewed the submitted medical records to ensure agreement with the adjudication. In a manner similar to that used in several large fracture studies, the adjudicator classified the reported fracture as follows: confirmed fracture, confirmed not to be a fracture, fracture uncertain, or insufficient documentation to determine.[16,17] 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; fracture-free survival, for which death as well as clinical fracture counted as an event; 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.[14] Before enrollment, we estimated the power of the trial to detect a clinically significant decrease in fracture risk. Assuming an enrollment of at least 5400 men over a period of 3.5 years, an additional 1.0 to 1.5 years of follow-up, and a fracture rate of 3 to 4% per year in the placebo group, we estimated that the trial would have at least 80% power to detect a 30% lower risk of fracture in the testosterone group than in the placebo group.

All event analyses of this subtrial were conducted in the full-analysis population that included all the participants who underwent randomization; the analyses were conducted on an intention-to-treat basis, irrespective of adherence to the trial regimen. Baseline characteristics were also assessed in the full-analysis population. In accordance with the prespecified analysis plan for the main trial, 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.

All analyses in the Fracture Trial used a cause-

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).

specific Cox proportional-hazards model with terms for trial group and status with respect to previous cardiovascular disease. Data from participants without an event were censored at the date of last contact. Prespecified sensitivity analyses are described in the Supplementary Appendix.[18]

Descriptive summaries of the adjudication process included the number and percentages of the total events reported. For fracture location and trauma, counts and percentages of participants having at least one event of the indicated type were calculated. Aalen–Johansen estimates of the cumulative incidence of fracture events, with death as a competing risk, were also computed.

In accordance with the statistical analysis plan, no adjustment was made for multiple comparisons. All confidence intervals are unadjusted and are not a substitute for hypothesis tests. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R software, version 4.2.1 (R Foundation for Statistical Computing).

RESULTS

PARTICIPANTS

Enrollment was conducted from May 23, 2018, to February 1, 2022. The last participant completed trial assessments on January 19, 2023. Of 5246 patient identification numbers, 42 were attributed to 20 participants with duplicate or triplicate enrollment. After excluding these, 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 baseline characteristics of the participants have been reported.[15] The two trial groups were similar with respect to age, race, serum testosterone and estradiol concentrations, and the use of medications to treat osteoporosis, which was documented in 13 participants (0.50%) in the testosterone group and 11 participants (0.42%) in the placebo group (Table S1 in the Supplementary Appendix). The trial participants appear to be representative of men with hypogonadism in this age range in the United States, except for an intentionally increased prevalence of cardiovascular disease (Table S2).

INTERVENTIONS AND ADHERENCE

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 (Fig. S1 and Table S3).

The median serum testosterone concentration in the testosterone group increased from 227 ng per deciliter (interquartile range, 189 to 258) (7.8 nmol per liter; interquartile range, 6.6 to 9.0) at baseline to 368 ng per deciliter (interquartile range, 266 to 519) (12.8 nmol per liter; interquartile range, 9.2 to 18.0) at month 6 and remained higher than baseline through year 3 (Table S4). The median serum testosterone concentration did not change substantially among the participants assigned to receive placebo. The median serum concentrations of dihydrotestosterone and estradiol (Tables S5 and S6) also increased among the participants assigned to receive testosterone but not among those assigned to receive placebo.

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)

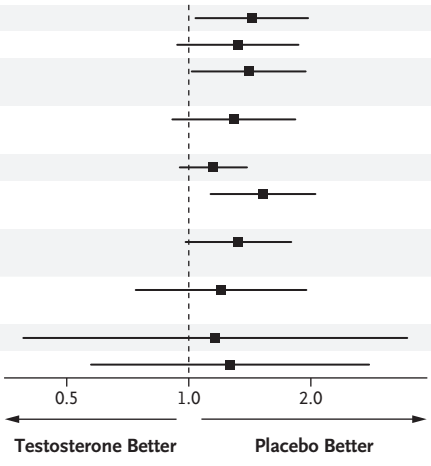

Figure 1. Fracture End Points.

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.

ADJUDICATION OF FRACTURES

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.

FRACTURE END POINTS

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) (Fig. 1). Results of prespecified sensitivity analyses were consistent with those of the primary analysis (Fig. S3). No departures from the proportional-hazards assumption were observed for any fracture end point. 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 (Fig. 2).

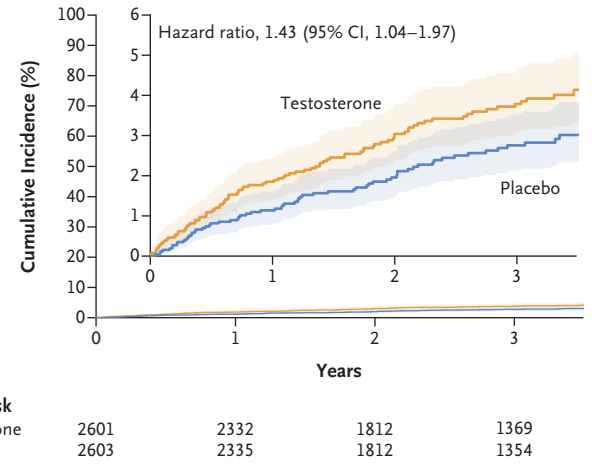

Figure 2. Cumulative Incidence of All Clinical Fractures.

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.

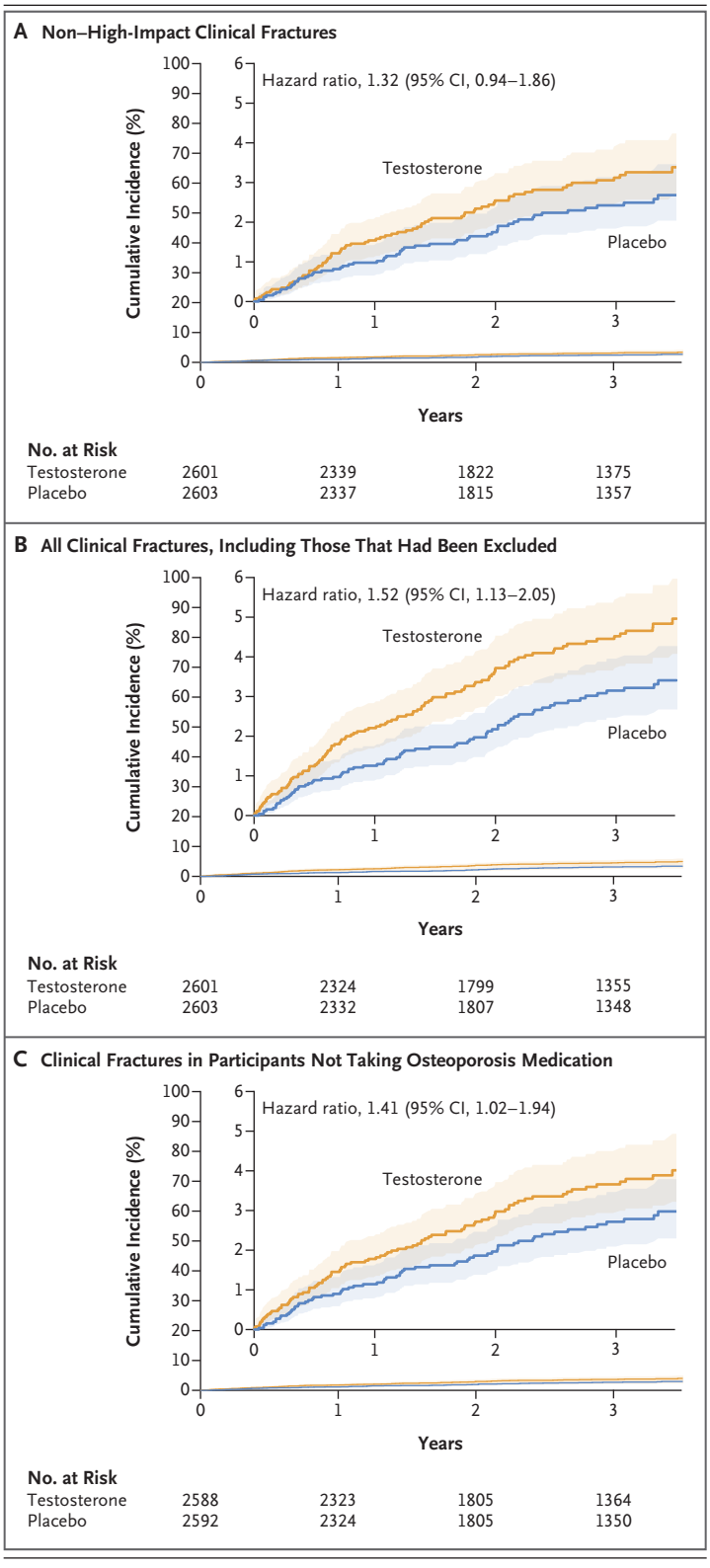

Figure 3. Cumulative Incidence of Three Types of Fractures.

Panel B includes data on fractures of the sternum, fingers, toes, facial bones, and skull, which were excluded from the analysis of all clinical fractures. In all panels, insets show the same data on expanded y axis. Pointwise 95% confidence interval bands are shown, as are the cause-specific hazard ratios with unadjusted 95% confidence intervals. 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.

TRAUMA, FRACTURE LOCATION, AND ADVERSE EVENTS

Most fractures in both trial groups were associated with trauma, more commonly with falls (Table 2). The anatomical locations of the fractures, including locations excluded from the primary analysis, are shown in Table S7. 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. Major adverse cardiovascular events, the primary end point of the parent trial, and all serious adverse events have been reported[15] and are summarized in Table S8.

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

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.

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.[19-21] The most common anatomical sites of fractures were ribs, wrist, and ankle, findings similar to those in previous studies involving men.[22,23] These sites are of clinical significance because fractures at these sites are associated with low bone mineral density[22-24] and with previous fractures[22,23] and are therefore considered osteoporotic fractures. More important, they are associated with an increased risk of future fractures[22] and increased mortality.[25]

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 density[1-4] and improved many structural and mechanical measures of trabecular bone on magnetic resonance microimaging.[5-7] In the Testosterone Trials, which involved older men with hypogonadism, testosterone treatment for 1 year increased volumetric bone mineral density and estimated bone strength on quantitative CT.[10]

Because we did not expect these results, we did not design the trial to assess possible mechanisms by which testosterone would increase the incidence of fractures, so we can only speculate about possible mechanisms. Although previous studies showed that testosterone treatment in men with hypogonadism improved many measures of bone structure, especially of trabecular bone, 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.[7]

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[26] and mood[26] and increased hemoglobin levels[27] 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.[15]

The Fracture Trial had many strengths, including enrolling more than 5000 men who had two low morning testosterone values, as well as a randomized, placebo-controlled design and a median duration of observation for more than 3 years — a large and long trial of testosterone treatment. Other strengths were the prespecified design to inquire about fractures at every visit, collection of information about reported fractures, and adjudication of the reported fractures centrally by an experienced adjudicator.[16,17]

This trial also had limitations. Participants were not evaluated for organic causes of hypogonadism, so it is not known whether some men with such causes were included. Adherence to administration of testosterone or placebo was suboptimal, although it was similar in the two trial groups. The increase in serum testosterone concentrations during treatment was less than in some other studies, but the lesser increase could not explain an increase in fractures. Information about falls was not assessed, except in participants who reported fractures. Physical activity and risk taking were also not assessed. Bone density and structure were not evaluated, so the effect of testosterone on these measures cannot be compared with the results in previous studies.

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.

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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.

REFERENCES

1. Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. J Clin Endocrinol Metab 1996;81:4358-65.
2. Snyder PJ, Peachey H, Berlin JA, et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000;85:2670-7.
3. Behre HM, Kliesch S, Leifke E, Link TM, Nieschlag E. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 1997;82:2386-90.
4. Leifke E, Körner HC, Link TM, Behre HM, Peters PE, Nieschlag E. Effects of testosterone replacement therapy on cortical and trabecular bone mineral density, vertebral body area and paraspinal muscle area in hypogonadal men. Eur J Endocrinol 1998;138:51-8.
5. Benito M, Vasilic B, Wehrli FW, et al. Effect of testosterone replacement on trabecular architecture in hypogonadal men. J Bone Miner Res 2005;20:1785-91.
6. Zhang XH, Liu XS, Vasilic B, et al. In vivo microMRI-based finite element and morphological analyses of tibial trabecular bone in eugonadal and hypogonadal men before and after testosterone treatment. J Bone Miner Res 2008;23:1426-34.
7. Al Mukaddam M, Rajapakse CS, Bhagat YA, et al. Effects of testosterone and growth hormone on the structural and mechanical properties of bone by micro-MRI in the distal tibia of men with hypopituitarism. J Clin Endocrinol Metab 2014;99:1236-44.
8. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004;89:503-10.
9. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 1999;84:1966-72.
10. 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.
11. Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154-64.
12. Smith MR, Lee WC, Brandman J, Wang Q, Botteman M, Pashos CL. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. J Clin Oncol 2005;23:7897-903.
13. Smith MR, Boyce SP, Moyneur E, Duh MS, Raut MK, Brandman J. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol 2006;175:136-9.
14. 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.
15. Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular safety of testosterone-replacement therapy. N Engl J Med 2023;389:107-17.
16. Black DM, Kelly MP, Genant HK, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med 2010;362:1761-71.
17. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 2006;296:2927-38.

18. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994; 81:515-26 (https://academic.oup.com/biomet/article-abstract/81/3/515/257037?redirectedFrom=fulltext).
19. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417-27.
20. Reid IR, Horne AM, Mihov B, et al. Fracture prevention with zoledronate in older women with osteopenia. N Engl J Med 2018;379:2407-16.
21. LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental vitamin D and incident fractures in midlife and older adults. N Engl J Med 2022;387:299-309.
22. Barrett-Connor E, Nielson CM, Orwoll E, Bauer DC, Cauley JA. Epidemiology of rib fractures in older men: Osteoporotic Fractures in Men (MrOS) prospective cohort study. BMJ 2010;340:c1069.
23. Wright NC, Hooker ER, Nielson CM, et al. The epidemiology of wrist fractures in older men: the Osteoporotic Fractures in Men (MrOS) study. Osteoporos IntApr 2018;29:859-70.
24. Chalhoub D, Orwoll ES, Cawthon PM, et al. Areal and volumetric bone mineral density and risk of multiple types of fracture in older men. Bone 2016;92:100-6.
25. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009;301:513-21.
26. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. N Engl J Med 2016;374:611-24.
27. 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.