Fracture risk

Testosterone treatment and fractures in men with hypogonadism

Snyder PJ *et al. N Engl J Med* 2024;390(3):203–11.

Background

- TTh is reported to improve bone density and quality in men with hypogonadism, but there are no long-term, randomised trials of a sufficiently large sample size and duration to evaluate the effect of TTh on the incidence of fractures in hypogonadal men
- The **TRAVERSE trial** was designed to determine the effects of TTh on the incidence of MACE among middle-aged and older hypogonadal men with either pre-existing CVD or who were at high CV risk; the **TRAVERSE Fracture substudy** evaluated whether TTh administration could reduce the risk of clinical fractures in this study population

Study type

- Phase 4, multicentre, randomised, double-blind, placebo-controlled, non-inferiority, event-driven trial (NCT03518034)

Patients

- TRAVERSE enrolled 5204 men aged 45–80 years with pre-existing CVD or elevated CV risk, who reported symptoms of hypogonadism plus two fasting testosterone levels <300 ng/dL (<10.4 nmol/L); osteoporosis was not an inclusion criterion
- 316 clinical trial sites in the USA

Interventions

- Randomisation 1:1 to daily transdermal 1.62% testosterone gel (n=2601), dose adjusted to maintain testosterone levels between 350–750 ng/dL (12.1–26.0 nmol/L), or matched placebo gel (n=2603) (**note:** a maximum dose of 101.25 mg was used, which is above the licensed maximum dose)

Fracture substudy outcome measures and analysis

- **Primary endpoint (time-to-event analysis):** time to first clinical fracture, defined as a clinical spine or non-spine fracture (not sternum, fingers, toes, facial bones or skull), documented by imaging or surgery and confirmed by adjudication
- **Secondary and exploratory endpoints included:** time to first non-high-impact clinical fracture; time to first clinical fracture in participants not taking a medication for osteoporosis; time to all clinical fractures; and time to any major osteoporotic fracture (hip, humerus, wrist or clinical spine)

Findings

- After a median follow-up of 3.19 years, a clinical fracture had occurred in 91 men (3.50%) in the TTh group and 64 men (2.46%) in the placebo group (HR 1.43; 95% CI: 1.04–1.97) (**Figure 1**)
- The cumulative incidence of clinical fracture at Year 3 was 3.8% (95% CI: 3.0–4.6) in the TTh group and 2.8% (95% CI: 2.1–3.5%) in the placebo group (**Figure 2**)
- TTh was also associated with a higher fracture incidence than placebo for other fracture end points (**Figure 1**)
- The majority of fractures in both treatment groups were associated with trauma, most commonly falls

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	Testosterone n/N (%)	Placebo n/N (%)	Hazard ratio for fracture (95% CI)
Primary: 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 men not taking osteoporosis medication	88/2588 (3.40)	63/2592 (2.43)	1.41 (1.02–1.94)
Non-high-impact fractures in men 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 were excluded	109/2601 (4.19)	72/2603 (2.77)	1.52 (1.13–2.05)
All clinical fractures, including those with uncertain/ 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)

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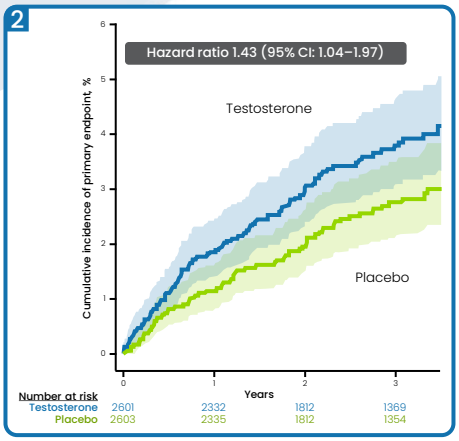

Conclusions

Among middle-aged and older men with hypogonadism, established CVD or multiple risk factors for incident cardiac events, TTh treatment did not result in a lower incidence of clinical fracture than placebo

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

Implications for the field

- The findings of the TRAVERSE Fracture substudy enable a more informed evaluation of the potential benefits and risks of TTh among middle-aged and older men with hypogonadism
- The increased incidence of fractures in study participants receiving TTh *vs* placebo may reflect that TTh enables an increase in physical activity, which may potentially lead to trauma and therefore more fractures

Abbreviations

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular events; TRAVERSE, Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men; TTh, testosterone therapy.

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