

Effect of testosterone replacement therapy on sexual function and hypogonadal symptoms in men with hypogonadism

Pencina KM *et al. J Clin Endocrinol Metab* 2023; doi: 10.1210/clinem/dgad484.

Background

- Few long-term randomised trials have evaluated the efficacy of TTh in improving sexual function and hypogonadal symptoms in men with hypogonadism, and whether effects are sustained beyond 12 months
- 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 Sexual Function substudy** evaluated the efficacy of TTh for improving sexual activity, hypogonadal symptoms, libido and erectile function among men in TRaverse who reported low libido

Study type

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

Patients

- Among 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), 1161 with low libido (DeRogatis Interview for Sexual Functioning – Desire score <20) were enrolled
- 316 clinical trial sites in the USA

Interventions

- Randomisation 1:1 to daily transdermal 1.62% testosterone gel (n=587), dose adjusted to maintain testosterone levels between 350–750 ng/dL (12.1–26.0 nmol/L), or matched placebo gel (n=574) (**note:** a maximum dose of 101.25 mg was used, which is above the licensed maximum dose)

Sexual Function substudy outcome measures and analysis

- Primary endpoint:** change from baseline in sexual activity score (assessed using the PDQ-4)
- Secondary endpoints included:** hypogonadal symptoms [by HIS-Q composite score (lower = fewer symptoms)], sexual function and sexual desire [by HIS-Q sexual function domain and libido subdomain], and erectile function (by IIEF-5)

PDQ-4: For all the items below, select yes if you have experienced (or are experiencing) today, otherwise select no

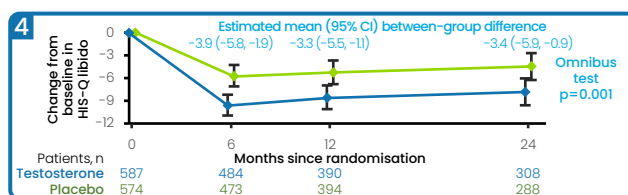
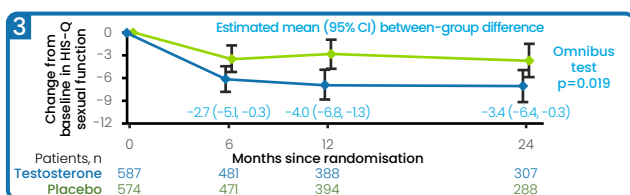
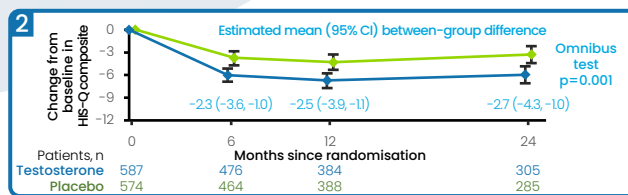
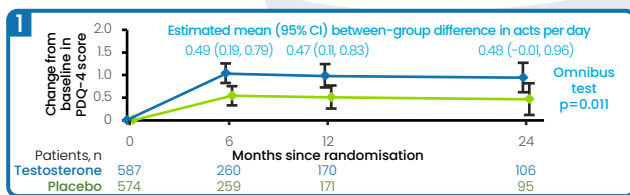
- | | |
|--|---|
| <input type="checkbox"/> Y <input type="checkbox"/> N Sexual daydreams | <input type="checkbox"/> Y <input type="checkbox"/> N Intercourse |
| <input type="checkbox"/> Y <input type="checkbox"/> N Anticipation of sex | <input type="checkbox"/> Y <input type="checkbox"/> N Masturbation |
| <input type="checkbox"/> Y <input type="checkbox"/> N Sexual interactions with partner | <input type="checkbox"/> Y <input type="checkbox"/> N Night spontaneous erection |
| <input type="checkbox"/> Y <input type="checkbox"/> N Flirting (by you) | <input type="checkbox"/> Y <input type="checkbox"/> N Day spontaneous erection |
| <input type="checkbox"/> Y <input type="checkbox"/> N Orgasm | <input type="checkbox"/> Y <input type="checkbox"/> N Night spontaneous erection |
| <input type="checkbox"/> Y <input type="checkbox"/> N Flirting (by others toward you) | <input type="checkbox"/> Y <input type="checkbox"/> N Erection in response to sexual activity |
| <input type="checkbox"/> Y <input type="checkbox"/> N Ejaculation | |

• **PDQ-4 score** is calculated as the average of the weekly values for all items (+1 for every yes and 0 for every no) at 6, 12 or 24 months since baseline

Lee KK *et al. J Androl* 2003;24:888–98

Findings

- In the Sexual Function substudy, compared with placebo, TTh was associated with significantly improved sexual activity (**Figure 1**), hypogonadal symptoms (**Figure 2**), sexual function (**Figure 3**) and sexual desire (**Figure 4**) (all $p < 0.05$), but not erectile function ($p = 0.443$), at 6, 12 and 24 months
- In the overall TRaverse population, hypogonadal symptoms, sexual symptoms and sexual desire were also significantly improved with TTh versus placebo (all $p < 0.001$)
- The observed treatment effects were irrespective of age ($\geq 65 / < 65$ years), prior CVD (yes/no), baseline testosterone level [$< 250 / \geq 250$ ng/dL ($< 8.7 / \geq 8.7$ nmol/L)] or race (White/Black American)



Conclusions

Among middle-aged and older men with hypogonadism and established CVD or multiple risk factors for incident cardiac events, who also reported low libido, TTh for 2 years improved sexual activity, hypogonadal symptoms and sexual desire, but not erectile function

Implications for the field

- The findings of the TRaverse Sexual Function substudy provide robust evidence on the efficacy of TTh for the treatment of reduced sexual function and hypogonadal symptoms in middle-aged and older men with hypogonadism, and enable a more informed evaluation of the potential benefits and risks of TTh in this population

Abbreviations

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HIS-Q, Hypogonadism Impact of Symptoms Questionnaire; IIEF-5, International Index of Erectile Function; MACE, major adverse cardiovascular events; PDQ-4, Psychosexual Daily Diary Question 4; TRaverse, Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men; TTh, testosterone therapy.

