Efficacy of testosterone replacement therapy in correcting anemia in men with hypogonadism: A randomized clinical trial

Pencina KM *et al. JAMA Netw Open* 2023;6(10):e2340030.

Background

- Few long-term randomised trials have evaluated the efficacy of TTh in preventing or correcting anaemia and improving 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 Anaemia substudy** evaluated the efficacy of TTh in correcting anaemia in men with hypogonadism and anaemia, and reducing the risk of developing anaemia in those without the condition

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), 815 men with anaemia and 4379 men without anaemia were enrolled
- 316 clinical trial sites in the USA

Interventions

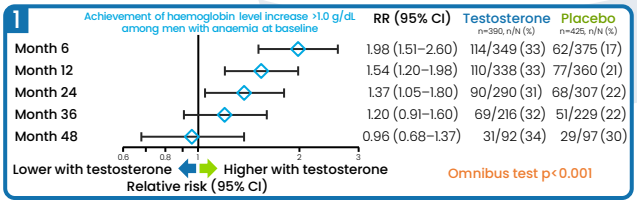
- Randomisation 1:1 to daily transdermal 1.62% testosterone gel (n=2593), dose adjusted to maintain testosterone levels between 350–750 ng/dL (12.1–26.0 nmol/L), or matched placebo gel (n=2601) (**note:** a maximum dose of 101.25 mg was used, which is above the licensed maximum dose)

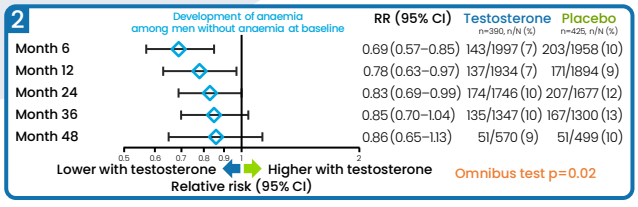
Anaemia substudy outcome measures and analysis

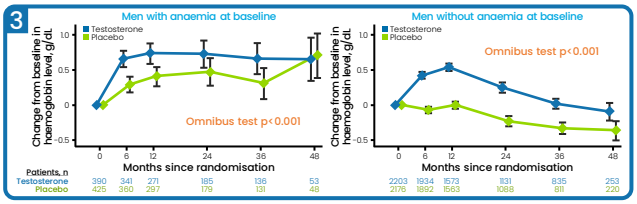
- **Primary endpoint:** correction of anaemia, defined as an increase in haemoglobin level ≥12.7 g/dL during the intervention period, among men with anaemia at baseline
- **Secondary endpoints included:** risk of developing anaemia in men without anaemia at baseline; proportion of men with anaemia whose haemoglobin level increased by >1.0 g/dL above baseline; change from baseline in haemoglobin level, haematocrit, red cell counts and indices, and HIS-Q energy and cognitive domain scores

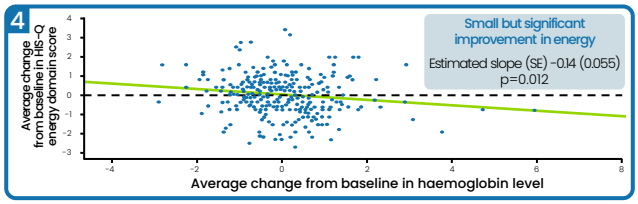
Findings

- Among men with anaemia, those receiving TTh were significantly more likely to experience correction of anaemia, and achieve a haemoglobin level increase >1 g/dL from baseline (**Figure 1**), compared with men receiving placebo
- Among men without anaemia, significantly fewer in the TTh group subsequently developed anaemia, compared with men in the placebo group (**Figure 2**)
- The observed treatment effects were irrespective of age (≥65/<65 years), prior CVD (yes/no), baseline testosterone level [<250/≥250 ng/dL (<8.7/≥8.7 nmol/L)] or race (White/Black or African American)
- Significant increases in haemoglobin level were observed in all men receiving TTh, compared with placebo (**Figure 3**), equating to a small but significant improvement in energy level (by HIS-Q energy domain score) (**Figure 4**)









Conclusions

Among middle-aged and older men with hypogonadism, established CVD or multiple risk factors for incident cardiac events, and anaemia, TTh for 2 years was more efficacious than placebo in correcting anaemia

Among men who were not anaemic, fewer TTh-treated men developed anaemia than did placebo-treated men

Implications for the field

- The findings of the TRAVERSE Anaemia substudy provide robust evidence on the efficacy of TTh for the prevention and correction of anaemia 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; MACE, major adverse cardiovascular events; RR, relative risk; TRAVERSE, Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men; TTh, testosterone therapy.