Diabetes

Effect of testosterone on progression from prediabetes to diabetes in men with hypogonadism: A substudy of the TRAVERSE randomized clinical trial

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Background

- Few long-term randomised trials have evaluated the effect of TTh on the risk of progression from prediabetes to diabetes in men with hypogonadism, or on inducing glycaemic remission in hypogonadal men with diabetes
- 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 Diabetes substudy** evaluated the efficacy of TTh for preventing progression from prediabetes to diabetes in hypogonadal men with prediabetes, and inducing glycaemic remission in hypogonadal men with diabetes

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), 1175 men with prediabetes and 3880 men with diabetes were enrolled
- 316 clinical trial sites in the USA

Interventions

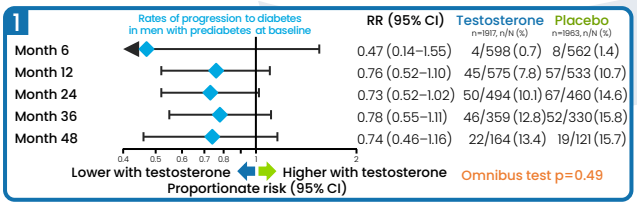
- Randomisation 1:1 to daily transdermal 1.62% testosterone gel (n=2601), dose adjusted to maintain testosterone levels between 350–750 ng/dL (12.1–26.0 nmol/L), or matched placebo gel (n=2603) (**note:** a maximum dose of 101.25 mg was used, which is above the licensed maximum dose)

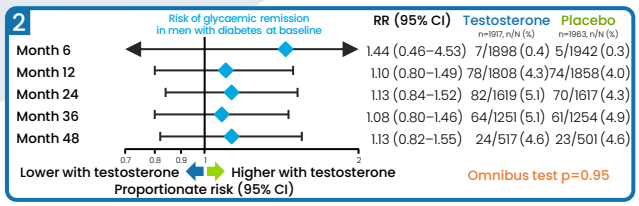
Diabetes substudy outcome measures and analysis

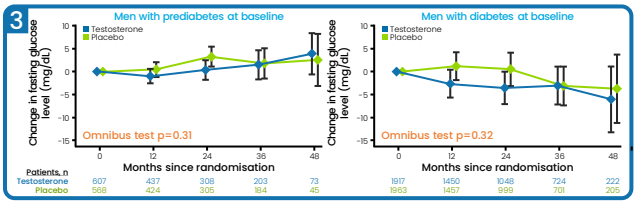
- **Primary endpoint:** risk of progression from prediabetes to diabetes (defined as HbA_{1c} ≥6.5%, initiation of diabetes medication, or 2 consecutive fasting glucose level measurements >125 mg/dL) in men with prediabetes at baseline
- **Secondary endpoints included:** risk of glycaemic remission (defined as HbA_{1c} <6.5% or 2 consecutive fasting glucose level measurements <126 mg/dL without current antidiabetic medication use) in men with diabetes at baseline; change from baseline in fasting glucose and HbA_{1c} levels in men with prediabetes or diabetes at baseline

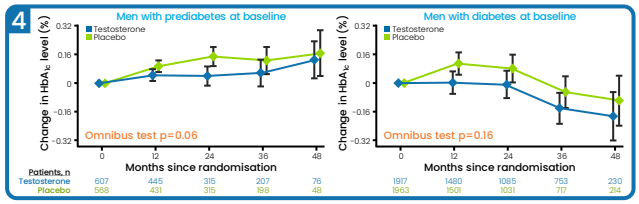
Findings

- Among men with prediabetes at baseline, no significant difference in relative risk of progression to diabetes was observed in those receiving TTh, compared with placebo (**Figure 1**)
- Among men with diabetes at baseline, no significant difference in glycaemic remission rates was observed in those receiving TTh, compared with placebo (**Figure 2**)
- The observed lack of treatment effects was 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)
- Change from baseline in fasting glucose or HbA_{1c} levels did not significantly differ between treatment groups in men with prediabetes or diabetes at baseline (**Figures 3** and **4**)









Conclusions

Among middle-aged and older men with hypogonadism, established CVD or multiple risk factors for incident cardiac events, and prediabetes or diabetes, TTh for up to 4 years did not significantly affect the risk of progression from prediabetes to diabetes, and did not improve glycaemic control in men with diabetes, versus placebo

Implications for the field

- The findings of the TRAVERSE Diabetes substudy provide robust evidence on the safety of TTh for the treatment of middle-aged and older men with hypogonadism, who may also have prediabetes or diabetes. These findings suggest that TRT alone should not be used as a therapeutic intervention to prevent or treat diabetes in men with hypogonadism.

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Abbreviations

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HbA_{1c}, glycated haemoglobin; MACE, major adverse cardiovascular events; RR, risk ratio; TRAVERSE, Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men; TTh, testosterone therapy.

TRAVERSE