CV safety

Cardiovascular safety of testosterone-replacement therapy

Lincoff AM *et al. N Engl J Med* 2023; doi: 10.1056/NEJMoa2215025.

Background

- In response to concerns and conflicting data on the CV safety of TTh, the FDA issued guidance on 3 March 2015 requiring manufacturers of approved testosterone products to conduct a clinical trial to determine if TTh increases the risk of heart attack or stroke
- **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

Study type

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

Patients

- 5246 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)
- 316 clinical trial sites in the USA

Interventions

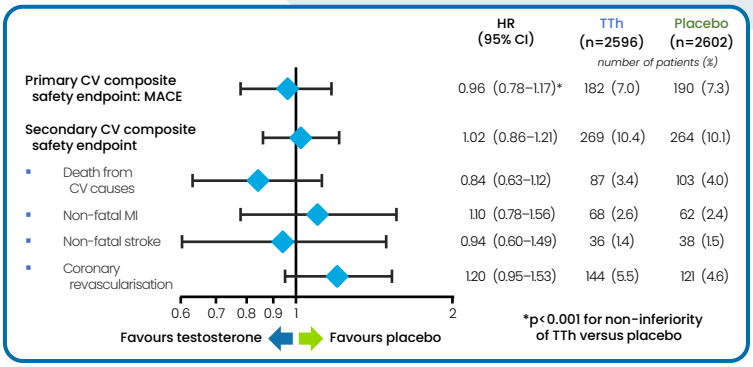
- Randomisation 1:1 to daily transdermal 1.62% testosterone gel (n=2596), dose adjusted to maintain testosterone levels between 350–750 ng/dL (12.1–26.0 nmol/L), or matched placebo gel (n=2602) (**note:** a maximum dose of 101.25 mg was used, which is above the licensed maximum dose)

Outcome measures and analysis

- **Primary CV composite safety endpoint:** first occurrence of MACE (death from CV causes, non-fatal MI or non-fatal stroke)
- **Secondary CV composite safety endpoint:** first occurrence of death from CV causes, non-fatal MI, non-fatal stroke, or coronary revascularisation
- All endpoints were assessed in a time-to-event analysis
- Non-inferiority required an upper limit of <1.5 for the 95% CI of the HR among patients receiving ≥1 dose of testosterone or placebo

Findings

- Patients were treated for 21.7 ± 14.1 months and followed up for 33.0 ± 12.1 months (both mean ± SD)
- A total of 61.4% and 61.7% of patients discontinued treatment in the TTh and placebo groups, respectively
- MACE (primary CV composite safety endpoint) occurred in 182 patients (7.0%) in the TTh group and 190 patients (7.3%) in the placebo group [**HR 0.96 (95% CI: 0.78–1.17); p<0.001 for non-inferiority of TTh versus placebo**]
- No clinically meaningful differences between treatment groups were apparent in the incidence of secondary CV safety endpoint events or the individual components of MACE
- No significant between-group differences were observed in AEs, except for non-fatal arrhythmias warranting intervention, atrial fibrillation and acute kidney injury, which occurred more often in the TTh group



% of patients	TTh	Placebo	p value
Any AE	45.7	44.7	0.47
SAE	27.8	26.8	0.42
AE leading to study drug discontinuation	9.4	8.7	0.37
AEs of special interest	7.6	6.4	0.11
▪ Hospitalisation for unstable angina	1.7	2.3	0.12
▪ Non-fatal arrhythmia	5.2	3.3	**0.001**
▪ CVD causing syncope	1.0	1.2	0.52
Diabetes	7.3	8.2	0.22
COVID-19	4.7	4.5	0.78
Atrial fibrillation	3.5	2.4	**0.02**
Acute kidney injury	2.3	1.5	**0.04**
Urinary retention	1.9	1.3	0.08

Conclusions

Among men with hypogonadism and established CVD or multiple risk factors for incident cardiac events, TTh was non-inferior to placebo with respect to the occurrence of MACE during a mean of 33 months of follow-up, and the overall incidence of AEs was low

Implications for the field

- The findings of the TRAVERSE study provide robust evidence on the CV safety of TTh for the treatment of middle-aged and older men with hypogonadism, and enable a more informed evaluation of the potential benefits and risks of TTh in this population

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Abbreviations

AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; CV, cardiovascular; CVD, cardiovascular disease; FDA, US Food and Drug Administration; HR, hazard ratio; MACE, major adverse cardiovascular events; SAE, serious adverse event; SD, standard deviation; TRAVERSE, Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men; TTh, testosterone therapy.

TRAVERSE