The TRAVERSE trial: cardiovascular safety of testosterone therapy for older men

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For decades, there has been controversy about whether testosterone therapy has deleterious effects on the risk of major cardiovascular events in older men. As the number of prescriptions for testosterone therapy has escalated, this controversy has heightened.[1] Although some epidemiological studies have suggested an association between testosterone therapy and risk of major cardiovascular events, an equal (or greater) number of epidemiological studies have demonstrated no increase or even a decreased risk associated with testosterone therapy.[2] Randomised trials have been underpowered,[3–7] but they have generally suggested that testosterone therapy at approximately physiological dosages did not increase the risk of major cardiovascular events for men (table).

The TRAVERSE study, published in 2023, was designed to address whether testosterone therapy was non-inferior to placebo for the risk of major cardiac events in men with established or at very high risk of coronary artery disease and a serum testosterone of less than 10·4 nmol/L in two early morning blood samples, and at least one symptom or sign that might be related to hypogonadism.[8] 5246 men were randomly assigned to transdermal testosterone or placebo gel, with a mean duration of 22 months and mean follow-up of 33 months. Although men aged 45–80 years were eligible, the mean age was 63, and 47% were older than 65 years. The participants' mean BMI was 35 kg/m^2, 70% had diabetes, and more than 90% had hypertension. The median serum total testosterone was 7·9 nmol/L. The primary outcome was the first occurrence of death from cardiac cause, non-fatal myocardial infarction, or non-fatal stroke. The primary analysis was conducted in the population of men who had been randomly assigned and administered at least one dose of testosterone or placebo. The primary sensitivity analysis included all major adverse cardiac events that occurred from initial randomisation to 365 days after the last dose. The investigators conducted supportive analyses and sensitivity analyses that corroborated the main findings.

No differences were found in the rate of a composite of adverse major cardiac events (HR 0·96, 95% CI 0·78–1·17) or in the individual secondary major cardiovascular outcomes; the Kaplan-Meier curves for the 4 years after randomisation were almost identical. In secondary analyses, there did not appear to be differences in secondary or tertiary cardiac outcomes, including death from any cause, coronary revascularisation, hospitalisation or urgent visit for heart failure, or overall venous thromboembolic events. There were additional findings that require further investigation and corroboration. Testosterone therapy was associated with a significantly higher incidence of non-fatal arrhythmias warranting interventions (5·2% in the testosterone group *vs* 3·3% in the placebo group) and atrial fibrillation (3·5% *vs* 2·3%). Testosterone therapy was also associated with an increased incidence of acute kidney injury (2·3% *vs* 1·5%), but the p value (0·04) was borderline significant.

There are important caveats to the TRAVERSE study.[8] First, the findings do not support the widespread practice of prescribing testosterone to young men and middle-aged men with vague symptoms and low-to-normal serum testosterone concentrations. Men in the TRAVERSE study had symptoms that might relate to androgen deficiency and very low serum total testosterone concentrations. The men who were randomly assigned to testosterone underwent strict dosage titration of transdermal testosterone to maintain serum total testosterone concentrations between 12·1 nmol/L to 26·0 nmol/L and to maintain a haematocrit of 54% or less. As a result of this meticulous adjustment, serum testosterone concentration increased modestly by about 5·2 nmol/L to a median of 13·0 nmol/L (with large IQRs). The TRAVERSE findings relating to the cardiovascular safety of physiological testosterone dosages in men with symptoms or signs of androgen deficiency and very low serum testosterone concentrations do not apply to eugonadal men who are taking pharmacological dosages that increase average serum testosterone concentrations above their baseline normal values. These safety findings might also not apply to hypogonadal men using testosterone formulations that result in considerably higher peak serum testosterone concentrations.