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Cardiovascular Safety of Testosterone Replacement Therapy in Hypogonadal Men

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About the Author

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Introduction

Testosterone replacement therapy (TRT) aims to restore serum testosterone levels in men with hypogonadism. Symptoms associated with hypogonadism include reduced libido, erectile dysfunction, fatigue, depression, and loss of muscle mass and bone density. The primary purpose of TRT is to alleviate these symptoms and improve quality of life by restoring serum testosterone levels to the physiological range.

The prevalence of hypogonadism in men increases with age, affecting approximately 2–5% of middle-aged and older men[1] and up to 20% of elderly men.[2] Despite its therapeutic benefits, the cardiovascular safety of TRT remains a topic of debate and investigation. Cardiovascular disease is a leading cause of morbidity and mortality among men, and any therapy that might influence cardiovascular risk requires careful evaluation. Early observational studies raised concerns about potential adverse cardiovascular outcomes associated with TRT. These findings prompted regulatory agencies to issue warnings and recommend further research. In response, more recent trials, including the TRAVERSE Study, have provided new insights into the relationship between TRT and cardiovascular health. This article aims to provide a review of recent evidence on the cardiovascular safety of TRT.

Physiological Role of Testosterone in Men

Testosterone influences numerous physiological processes, including muscle mass maintenance, bone density, libido, and mood regulation. Endogenously produced testosterone contributes to cardiovascular health by promoting vasodilation, modulating lipid profiles, and enhancing insulin sensitivity.[3]

Mechanisms of Testosterone's Influence on Cardiovascular Health

The mechanisms by which testosterone may influence cardiovascular health are complex and multifactorial. Testosterone is believed to exert both beneficial and potentially adverse effects on the cardiovascular system.

Vascular Function. The vasodilatory effects of testosterone contribute to its potential benefits in improving blood flow and reducing blood pressure. Testosterone stimulates the production of nitric oxide in endothelial cells, which in turn activates guanylate cyclase, increasing cyclic guanosine monophosphate levels, leading to muscle relaxation and vessel dilation. Testosterone can also modulate calcium channels in vascular smooth muscle cells, decreasing muscle contraction and promoting vasodilation by reducing intracellular calcium concentrations.[3]

Lipid Metabolism. Impact on lipid parameters in response to TRT has been mixed. Studies in hypogonadal healthy men, men with cardiovascular disease, metabolic syndrome and Type 2 diabetes (T2DM) show decrease in total cholesterol and low-density lipoprotein (LDL) by 5–14% from baseline with TRT. However, other studies have shown no effect. Similarly, HDL levels vary from increased to decreased to unchanged with TRT.[3] Proposed mechanisms for favourable changes in lipid profile include reduced *de novo* lipogenesis in adipose and liver tissue in response to testosterone. Testosterone also inhibits lipoprotein lipase activity and subsequent lower availability of free fatty acids in the bloodstream for uptake by tissues.[3]

Insulin Sensitivity. Hypogonadal men with T2DM and/or metabolic syndrome showed TRT- reduced homeostatic mechanism of insulin resistance by 15%.[4] This effect was confirmed using hyperinsulinemic euglycemic clamp studies, showing a 32% increase in glucose uptake after 6 months of TRT in men with T2DM and hypogonadotropic hypogonadism. The increase in insulin sensitivity was not related to change in lean mass, subcutaneous fat or visceral fat. However, expression of insulin signaling genes (IR-β, IRS-1, AKT-2, and GLUT4) was upregulated by more than 50% in adipose tissue after testosterone treatment compared with placebo.[5]

Conversely, testosterone can also stimulate erythropoiesis, potentially leading to increased blood viscosity and a higher risk of thromboembolic events. Graded doses of testosterone on erythropoiesis in healthy young and older men demonstrated that testosterone has a dose-dependent stimulatory effect on erythropoiesis. Both hemoglobin and hematocrit levels increased significantly in a linear fashion in response to testosterone doses, with older men showing a more pronounced response compared to younger men.[6]

Historical Perspective on TRT and Cardiovascular Risk

Initial observational studies and retrospective analyses suggested an association between TRT and increased cardiovascular events, such as myocardial infarction and stroke[7-9]. These findings led regulatory agencies like the FDA to mandate more rigorous safety labelling for testosterone products, emphasizing the potential risks.[10] These concerns led to a surge in research aimed at elucidating the true cardiovascular risks associated with TRT.

Recent large-scale trials studies, including the TRAVERSE study, have sought to address these concerns by providing more robust data on the cardiovascular outcomes of men undergoing TRT.

TRAVERSE Study

The TRAVERSE Study is one of the most extensive clinical trials to date investigating the cardiovascular safety of testosterone replacement therapy (TRT) in men with hypogonadism.[11]

Study Design and Population

This multicentre, randomized, double-blind, placebo-controlled trial included 5246 men aged 45 to 80 with symptomatic hypogonadism and either preexisting CV disease (CAD, CVD or PAD) or increased risk of CV disease (3 or more CV risk factors including hypertension, dyslipidemia, current smoking, stage 3 kidney disease, diabetes, elevated high sensitivity C-reactive protein, age 65 years or older, documented historical Agatston coronary calcium score greater than 75th percentile for age and race). Participants received either testosterone or a placebo gel, applied daily for a mean (±SD) duration of treatment of 21.7±14.1 months, and mean follow-up of 33.0±12.1 months). The primary endpoint was the occurrence of MACE, defined as a composite of myocardial infarction, stroke or cardiovascular-related death. Secondary endpoints included individual components of the

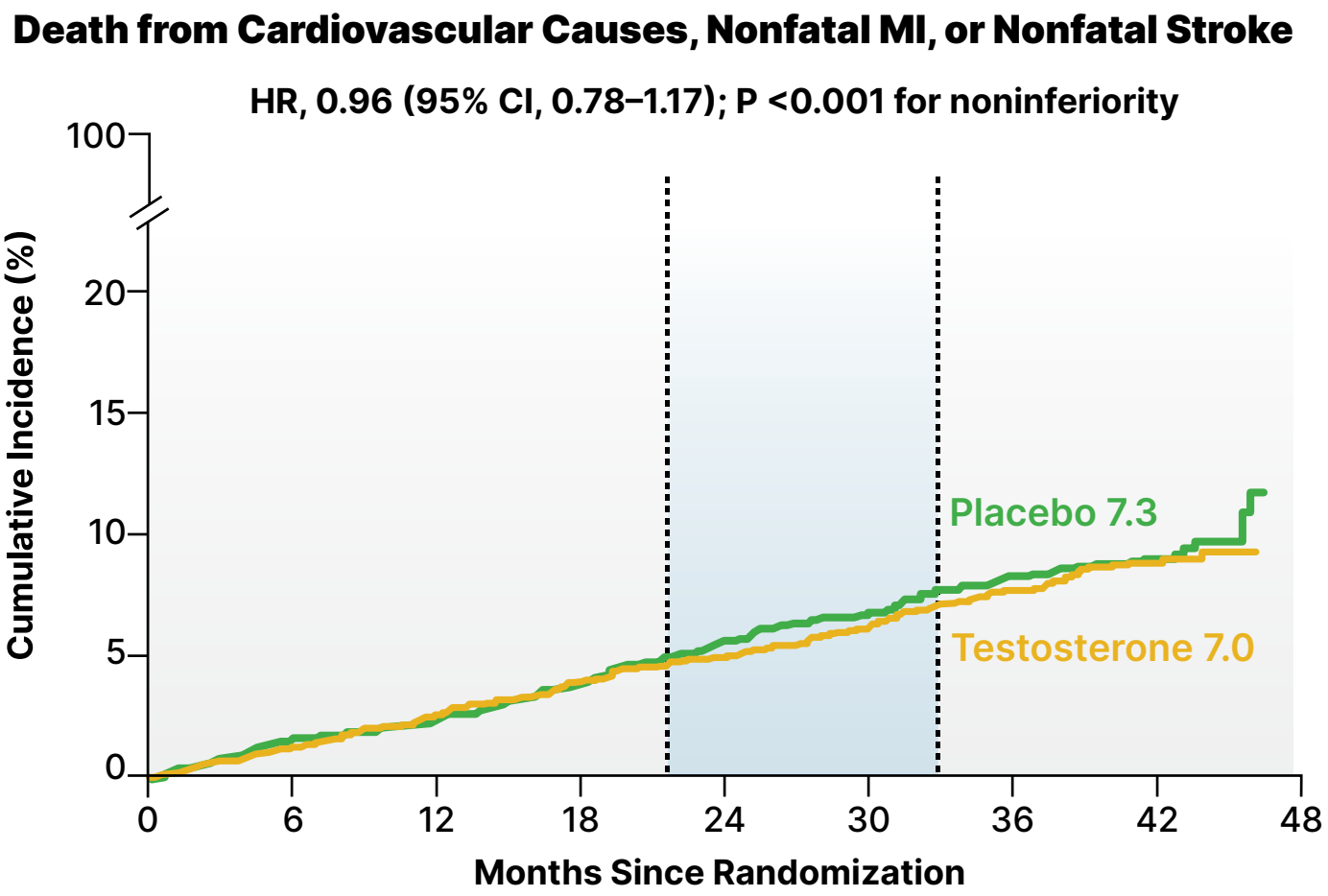

Figure 1. Incidence of major adverse cardiovascular events (MACE) in the TRAVERSE study; *adapted from Lincoff, AM, et al., 2023.*

primary endpoint, as well as other cardiovascular outcomes such as hospitalization for heart failure and coronary revascularization.

Results

The study found that the incidence of MACE was not significantly different between the testosterone and placebo groups. Specifically, 182 participants (7.0%) in the testosterone group experienced a MACE compared to 190 participants (7.3%) in the placebo group (HR 0.96; 95% CI, 0.78 to 1.17). The incidence rates of the primary endpoint were similar between the testosterone and placebo groups, suggesting that TRT does not exacerbate the risk of major cardiovascular events in this high-risk population. These results are pivotal, as they provide reassurance about the cardiovascular safety of TRT when administered under controlled conditions to appropriately selected men.

Adverse Events

While the TRAVERSE Study largely supports the cardiovascular safety of TRT, it also evaluated several adverse events associated with testosterone therapy. The study reported increased prostate-specific antigen (PSA) levels in the TRT group (P <0.001). Non-fatal arrhythmias warranting intervention, as well as atrial fibrillation, were significantly higher in the TRT group (5.2% vs. 3.3%, 3.5% vs. 2.4% respectively). Acute kidney injury occurred in 2.3% of the TRT group and 1.5% of the placebo group. The incidence of pulmonary embolism was also higher with testosterone than with placebo (0.9% vs. 0.5%, respectively).[11]

In addition to cardiovascular outcomes, the TRAVERSE Study examined bone health and fracture risk among participants. Bone density measurements indicated that TRT was associated with increased bone mineral density (BMD) at the lumbar spine and hip, suggesting potential benefits for skeletal health. However, despite these improvements in BMD, there

was an unexpected increase in the incidence of fractures in the TRT group compared to the placebo group. The fracture rate was 3.5% in the TRT group vs. 2.46% in the placebo group (HR 1.43, 95% CI, 1.04 to 1.97). Most fractures in both groups were associated with trauma, more commonly with falls, most commonly affecting the ribs, wrist and ankle[12]. This finding indicates a potential area of concern and suggests that while cardiovascular risks may not be heightened, other risks such as bone health require further investigation and careful management in clinical practice.

Testosterone Trials (TTrials)[13]

The Testosterone Trials consist of a series of seven coordinated trials aimed at determining the efficacy and safety of TRT in older men with low testosterone levels. These trials encompass various health aspects, including sexual function, physical function, vitality, cognitive function, bone density, anemia, and cardiovascular health. The Cardiovascular Trial within the TTrials specifically assessed the impact of TRT on coronary artery plaque volume (**Table 1**).

The cardiovascular trial involved 170 men aged 65 and older who were randomly assigned to receive either testosterone gel or a placebo for one year. The primary outcome measured was the change in coronary artery plaque volume, assessed through coronary computed tomography angiography. No participants in the treatment or placebo group were reported to have a major adverse cardiovascular event.

The results indicated a significant increase in non-calcified plaque volume in men receiving TRT compared to those receiving placebo. However, these findings were not associated with an increased incidence of cardiovascular events during the study period, warranting further investigation into the long-term implications.

T4DM Trial[14]

The Testosterone for Diabetes Mellitus (T4DM) trial was a randomized, double-blind, placebo-controlled trial. The primary objective was to evaluate whether or not testosterone therapy combined with lifestyle intervention could reduce the incidence of T2DM in men at high risk. The study included 1007 men aged 50–74 years with a waist circumference of >95 cm who had impaired glucose tolerance or newly diagnosed T2DM had low testosterone levels.

The participants were randomly assigned to receive either testosterone therapy or a placebo, alongside a structured lifestyle program. Over the two-year study period, the results demonstrated that the group receiving testosterone therapy had a significantly reduced risk of developing T2DM compared to the placebo group. There was no significant difference in the incidence of cardiovascular events between the TRT and the placebo group. This finding suggests that testosterone therapy did not increase the risk of cardiovascular events over the two-year study period. Additionally, the testosterone group experienced significant improvements in body composition, insulin sensitivity, and glycemic control, which are beneficial factors for cardiovascular health.

TEAAM Trial[15]

The Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) trial investigated the impact of TRT on atherosclerosis progression in older men. This double-blind, placebo-controlled trial enrolled 308 men aged 60 years or older with low or low-normal testosterone levels and followed them for three years. Co-primary outcomes included carotid artery intima-media thickness and coronary artery calcium score.

The study found no significant difference between the TRT and placebo groups, suggesting that TRT does not accelerate atherosclerosis progression in older men.

Discussion

The cardiovascular safety of TRT has been a contentious issue, with early studies suggesting increased risks and more recent trials providing reassuring evidence. While recent trials have provided valuable insights into the cardiovascular safety of TRT, several areas warrant further research. Long-term studies are needed to assess the impact of TRT on cardiovascular outcomes in diverse populations, including men with varying degrees of cardiovascular risk.

The TRAVERSE Study revealed several unexpected adverse events in the testosterone treatment group, including an increased incidence of fractures, atrial fibrillation, and nonfatal arrhythmias. These findings raise concerns about the comprehensive safety profile of TRT and underscore the need for further investigation. While TRT has demonstrated benefits in symptom

Study Name	Study Design and Methods	Age of Study Population	Baseline Testosterone Levels (*nmol/L*)	Testosterone Administered	Study Duration	Cardiovascular Outcomes	Adverse Events
TRAVERSE Study	Randomized, double-blind, placebo-controlled	45-80 years	≤10.4	1% testosterone gel daily	3 years	No significant difference in incidence of MACE between testosterone and placebo groups (HR 0.96; 95% CI, 0.78–1.17)	Increased PSA. Increased incidence of arrhythmia, atrial fibrillation, pulmonary embolism, fractures, and acute kidney injury
Cardiovascular T Trial	Randomized, double-blind, placebo-controlled	≥65 years	≤9.5	Testosterone gel	1 year	Increased non-calcified coronary artery plaque volume in testosterone group (P=0.003); no difference in MACE	Increased hemoglobin and hematocrit levels in the testosterone group
TEAAM Trial	Randomized, double-blind, placebo-controlled	≥60 years	3.46–13.9	Testosterone gel	3 years	No significant effect on progression of subclinical atherosclerosis measured by carotid artery intima-media thickness (CIMT) and coronary artery calcium (CAC)	Increased erythrocytosis and PSA in testosterone group
T4DM Trial	Randomized, double-blind, placebo-controlled	50–74 years	≤14.0	1000 mg testosterone undecanoate every 3 months	2 years	Reduced incidence of T2D (RR 0.59; 95% CI, 0.43–0.80). No significant increase in MACE.	Increased risk of erythrocytosis

Table 1. Summary of key cardiovascular trials on testosterone replacement therapy; *courtesy of Jagoda Kissock, MD, FRCPC.*

relief and metabolic health improvements, the emergence of these adverse events suggests a more complex risk-benefit landscape that must be thoroughly evaluated.

Future research should focus on identifying the patient populations at highest risk for these adverse events and elucidating the underlying pathophysiological mechanisms. Longitudinal studies with larger sample sizes and extended follow-up periods are necessary to assess the long-term cardiovascular and skeletal impacts of TRT. Additionally, examining the role of various testosterone formulations and dosing regimens in modulating these risks could provide valuable insights for optimizing treatment regimens.

Conclusion

The cardiovascular safety of TRT in men remains a critical concern for clinicians. Recent studies, including the TRAVERSE study, provide reassuring evidence that TRT does not significantly increase the risk of cardiovascular events in men with hypogonadism. However, careful patient selection, monitoring and individualized treatment approaches are essential to minimize potential risks and maximize benefits. Continued research is needed to further elucidate the long-term cardiovascular effects of TRT and guide clinical practice.

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