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Testosterone Therapy and Cardiovascular Disease: The TRAVERSE Trial

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Introduction

A thorough literature review affirms that in males with testosterone deficiency (TD), testosterone therapy (TTh) improves clinical outcomes including body composition,[1,2,3,4,5,6,7] sexual function,[8,9,10,11,12] and bone mineral density (BMD).[13,14,15,16,17,18,19,20] In males with TD, TTh does not increase prostate cancer (PC)[21,22,23,24,25,26,27] and the literature suggests that not only is TTh safe for the cardiovascular system, but it may also decrease myocardial infarction (MI) and mortality rates.[28,29,30,31,32,33,34,35,36,37,38]

Between 2010 and 2014, four published studies raised concerns about TTh and cardiovascular (CV) risk. These studies suggested that TTh increased CV risk. These 4 studies received an unusual amount of media attention and provided talking points for those who believed that TTh was unnecessary or dangerous. Two studies were retrospective analyses (Vigen[39] and Finkle[40]), 1 was a meta-analysis (Xu[41]), and one was a randomized controlled trial (Basaria[42]). These 4 studies led the FDA to mandate a label change to all T products warning against possible MI and stroke. Since then, male health experts have questioned these studies' validity, accuracy, and credibility.[43,44,45,46,47]

There are numerous observational trials, clinical trials, and metanalyses that have not demonstrated an association between TTh and cardiovascular risk.[28-31] In fact, some studies suggest TTh may be cardioprotective,[32-35,37,38] though more studies are needed to confirm that TTh improves CAD and CV outcomes.

TRAVERSE Trial[48]

Until the recently published TRAVERSE trial, there were no large, randomized, double-blind, placebo-controlled published trials (RCTs) evaluating TTh and cardiovascular outcomes. TRAVERSE (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men) was a multicenter, randomized, double-blind, placebo-controlled, noninferiority trial that enrolled 5246 males, 45 to 80 years old, with either documented cardiovascular disease or a high risk for cardiovascular disease (> 3 cardiovascular risk factors).

All male participants had one or more testosterone deficiency symptom (decreased libido or sexual desire, decreased spontaneous erections, etc.) and 2 fasting total testosterone levels < 300ng/dL obtained between 5 AM and 11 AM using a liquid chromatography-tandem mass spectrometry assay.

Males were randomized in a 1:1 ratio to receive AndroGel or matching placebo. The patient demographics were similar in both groups. The study included 2847 males with preexisting cardiovascular disease and 2357 males with an elevated cardiovascular risk. The mean testosterone daily dose was 65mg. Dose adjustments were made to maintain serum trough total testosterone levels between 350 and 750ng/dL or to respond to a hematocrit level > 54%.

The mean treatment duration and follow-up were 21.7 and 33 months. In the treatment arm, the mean trough total testosterone levels ranged from 387-432ng/dL with mean estradiol levels of 31-32pg/mL. In the placebo arm, the mean trough total testosterone levels ranged from 230-264ng/dL with mean estradiol levels of 19-20pg/mL.

There was no statistically significant difference between the treatment arm (7.0%) and the placebo arm (7.3%) in the primary safety endpoint. The primary safety endpoint was the first occurrence of any component of major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, death due to cardiovascular causes) and/or a composite of death from cardiovascular causes.

However, pulmonary embolism occurred at a higher incidence in the testosterone treatment group (0.9%) vs the placebo group (0.5%). In the treatment arm, there was also a statistically significant increase in nonfatal arrhythmias warranting intervention, atrial fibrillation, and acute kidney injury when compared to the placebo arm.

The authors concluded that in testosterone-deficient males aged 45-80 with documented cardiovascular disease or at high cardiovascular risk, testosterone-replacement therapy was noninferior to placebo with respect to major adverse cardiovascular events.

Discussion

TRAVERSE targeted a very specific male patient population. Males aged 45-80 with known cardiovascular disease or males at high risk for cardiovascular disease. AndroGel was utilized and the total testosterone ranges were trough levels similar to trough levels that have been used in previous RCTs[28-31] and observational studies[32-38] that documented improved cardiovascular outcomes.

What is concerning, and certainly needs further study, is the increased incidence, in this patient population, of pulmonary embolism, nonfatal arrhythmias warranting intervention, atrial fibrillation, and acute kidney injury when compared to the placebo arm. Therefore, until further studies are performed, caution should be used, and patients should be counselled, when considering testosterone therapy in this male population with a prior venous thromboembolic event (DVT, PE), a history of acute kidney injury, and/or a history of atrial fibrillation or other nonfatal arrhythmias.

Conclusion

TRAVERSE documented that testosterone therapy is safe and does not increase major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, death due to cardiovascular causes, or a composite of death from cardiovascular causes) in testosterone-deficient males with cardiovascular disease or in males at high risk for cardiovascular disease. Screening for thromboembolic disease, a history of acute kidney injury, and/or a history of atrial fibrillation or other nonfatal arrhythmias should allow clinicians to minimize these potential adverse events.

Moreso, it is plausible that in testosterone-deficient males without cardiovascular disease or cardiovascular risk factors, testosterone-replacement therapy is safe if serum total trough testosterone levels are maintained within a similar range.

[1] Wang C, et al. Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men. J Clin Endocrinol Metab. 2000; 85(8): 2839-2853.

[2] Wang C, et al. Long-Term Testosterone Gel (AndroGel) Treatment Maintains Beneficial Effects on Sexual Function and Mood, Lean and Fat Mass, and Bone Mineral Density in Hypogonadal Men. J Clin Endocrinol Metab. 2004; 89(5): 2085-2098.

[3] Saad F, et al. Long-Term Treatment of Hypogonadal Men with Testosterone Produces Substantial and Sustained Weight Loss. Obesity (Silver Spring). 2013; 21(10): 1975-1981.

[4] Saad F, et al. Effects of long-term treatment with testosterone on weight and waist size in 411 hypogonadal men with obesity classes I-III: observational data from two registry studies. Int J Obes (Lond). 2016; 40(1): 162-170.

[5] Traish AM, et al. Long-Term Testosterone Therapy Improves Cardiometabolic Function and Reduces Risk of Cardiovascular Disease in Men with Hypogonadism: A Real-Life Observational Registry Study Setting Comparing Treated and Untreated (Control) Groups. Cardiovasc Pharmacol Ther. 2017; 22(5): 414-433.

[6] Corona G, et al. Testosterone supplementation and body composition: results from a meta-analysis of observational studies. J Endocrinol Invest. 2016; 39(9): 967-981.

[7] Corona G, et al. Testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol. 2016; 174(3): R99-116.

[8] Rastrelli G, et al. Testosterone and sexual function in men. Maturitas. 2018; 112:46-52.

[9] O'Connor DB, et al. The Relationships between Sex Hormones and Sexual Function in Middle-Aged and Older European Men. J Clin Endocrinol Metab. 2011; 96(10): E1577-1587.

[10] Cunningham GR, et al. Testosterone Treatment and Sexual Function in Older Men With Low Testosterone Levels. J Clin Endocrinol Metab. 2016 Aug;101(8):3096-3104.

[11] Corona G, et al. Meta-analysis of Results of Testosterone Therapy on Sexual Function Based on International Index of Erectile Function Scores. Eur Urol. 2017; 72(6): 1000-1011.

[12] Brock G, et al. Effect of Testosterone Solution 2% on Testosterone Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study. J Urol. 2016; 195(3): 699-705.

[13] Golds G, et al. Male Hypogonadism and Osteoporosis: The Effects, Clinical Consequences, and Treatment of Testosterone Deficiency in Bone Health. Int J Endocrinol. 2017; 2017: 4602129.

[14] Haider A. Progressive Improvement of T-Scores in Men with Osteoporosis and Subnormal Serum Testosterone Levels upon Treatment with Testosterone over Six Years. Int J Endocrinol. 2014; 2014: 496948.

[15] Snyder PJ, et al. Effect of Testosterone Treatment on Volumetric Bone Density and Strength in Older Men With Low Testosterone: A Controlled Clinical Trial. JAMA Intern Med. 2017; 177(4): 471-479.

[16] Finkelstein JS, et al. Gonadal steroid–dependent effects on bone turnover and bone mineral density in men. J Clin Invest. 2016; 126(3): 1114-1125.

[17] Vanderschueren D, et al. Sex Steroid Actions in Male Bone. Endocr Rev. 2014; 35(6): 906-960.

[18] LeBlanc ES, et al. The Effects of Serum Testosterone, Estradiol, and Sex Hormone Binding Globulin Levels on Fracture Risk in Older Men. J Clin Endocrinol Metab. 2009; 94(9): 3337-3346.

[19] Cauley JA, et al. Sex Steroid Hormones in Older Men: Longitudinal Associations with 4.5-Year Change in Hip Bone Mineral Density—The Osteoporotic Fractures in Men Study. J Clin Endocrinol Metab. 2010; 95(9): 4314-4323.

[20] Cawthon PM, et al. Sex Hormones, Sex Hormone Binding Globulin, and Vertebral Fractures in Older Men. Bone. 2016; 84: 271–278.

[21] Morgentaler A, Traish AM. Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth. Eur Urol. 2009; 55(2): 310-320.

[22] Khera M, et al. A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications. Eur Urol. 2014; 65(1): 15-23.

[23] Schenk JM, et al. Serum androgens and prostate cancer risk: results from the placebo arm of the Prostate Cancer Prevention Trial. Cancer Causes Control. 2016; 27(2): 175-182.

[24] Cui Y, et al. The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2014; 17(2): 132-143.

[25] Loeb S, et al. Testosterone Replacement Therapy and Risk of Favorable and Aggressive Prostate Cancer. J Clin Oncol. 2017; 35(13):1430-1436.

[26] Baillargeon J, et al. Long-term Exposure to Testosterone Therapy and the Risk of High Grade Prostate Cancer. J Urol. 2015; 194(6): 1612-1616.

[27] Wallis CJD, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study. Lancet Diabetes Endocrinol. 2016; 4(6): 498-506.

[28] Snyder PJ, et al. Lessons from the Testosterone Trials. Endocr Rev. 2018; 39(3): 369-386.

[29] Basaria S, et al. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels. JAMA. 2015; 314(6): 570-581.

[30] Snyder PJ, et al. Effects of Testosterone Treatment in Older Men. N Engl J Med. 2016; 374(7): 611–624.

[31] Budoff MJ, et al. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. JAMA. 2017; 317(7): 708-716.

[32] Sharma R, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J. 2015; 36(40): 2706-2715.

[33] Anderson JL, et al. Impact of Testosterone Replacement Therapy on Myocardial Infarction, Stroke, and Death in Men With Low Testosterone Concentrations in an Integrated Health Care System. Am J Cardiol. 2016; 117(5): 794-799.

[34] Wallis CJ, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study. Lancet Diabetes Endocrinol. 2016; 4(6): 498-506.

[35] Cheetham TC. Association of Testosterone Replacement With Cardiovascular Outcomes Among Men With Androgen Deficiency. JAMA Intern Med. 2017; 177(4):491-499.

[36] Araujo A, et al. Endogenous Testosterone and Mortality in Men: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2011; 96(10): 3007-3019.

[37] Shores MM, et al. Testosterone Treatment and Mortality in Men with Low Testosterone Levels. J Clin Endocrinol Metab. 2012; 97(6): 2050-2058.

[38] Muraleedharan V, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol. 2013; 169(6): 725-733.

[39] Vigen R, et al. Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels. JAMA. 2013; 310(17): 1829-1836.

[40] Finkle WD, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One. 2014; 9(1): e85805.

[41] Xu L, et al. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med. 2013; 11: 108.

[42] Basaria S, et al. Adverse Events Associated with Testosterone Administration. N Engl J Med. 2010; 363(2): 109-122.

[43] Morgentaler A, et al. Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International ExpertConsensus Resolutions. Mayo Clin Proc. 2016; 91(7): 881-896.

[44] Traish A. Testosterone therapy in men with testosterone deficiency: are the benefits and cardiovascular risks real or imagined? Am J Physiol Regul Integr Comp Physiol. 2016; 311(3): R566-573.

[45] Morgentaler A, Traish AM. The history of Testosterone and the Evolution of its Therapeutic Potential. Sex Med Rev. 2020; 8(2): 286-296.

[46] Morgentaler A, et al. Testosterone Therapy and Cardiovascular Risk: Advances and Controversies. Mayo Clin Proc. 2015; 90(2): 224-251.

[47] Miner M, et al. The state of testosterone therapy since the FDA's 2015 labelling changes: Indications and cardiovascular risk. Clin Endocrinol (Oxf). 2018; 89(1): 3-10.

[48] Lincoff AM, et al. Cardiovascular Safety of Testosterone-Replacement Therapy. N Engl J Med. 2023. Doi: 10.1056/NEJMo2215025