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Testosterone Therapy and Cardiovascular Risk: A Critical Analysis of Studies Reporting Increased Risk

Mohit Khera, MD, MBA, MPH,[1] Martin Miner, MD,[2] Jonathan Jaffe, MD,[3] and Alexander W. Pastuszak, MD, PhD[4]

ABSTRACT

Background: Treatment of "adult-onset hypogonadism" (AOH) with exogenous testosterone therapy (TTh) to raise serum testosterone (T) levels may influence cardiovascular (CV) risk factors in patients with AOH, whereas low endogenous T levels are associated with an increased CV risk and mortality.

Aim: To critically evaluate studies reporting increased CV risk associated with TTh and to provide an overview of the risks and benefits of restoring T levels through exogenous TTh.

Methods: A review of publications focusing on the association between TTh and increased CV risk was conducted, and the study methodologies and conclusions of each were critically evaluated. Further, recent clinical and epidemiological studies associating AOH or TTh with a change in CV risk, and pertinent hematologic and vascular effects noted in animal studies and *in vitro*, as well as in clinical practice were also reviewed.

Outcomes: A review of the literature shows that untreated testosterone deficiency and/or low T is associated with an increase in CV risk and adverse outcomes, with numerous studies and meta-analyses to support a positive association between exogenous TTh and an improvement in CV risk factors in men with AOH.

Results: Numerous studies in the literature demonstrate the positive benefits of using TTh; however, since 2013, some publications have suggested a link to increased CV risk associated with TTh. A number of these studies retrospectively analyzed insurance claims databases using diagnosis codes, procedures codes, and prescription information. Many reviews published since have pointed out the methodological flaws and debatable conclusions of these studies.

Clinical Implications: A careful assessment of the patient's current health status and CV risk factors should be weighed against the benefits and possible risks resulting from TTh, and consideration should be given to deferring treatment pending resolution or stabilization of CV disease or risk factors.

Strengths & Limitations: In this review, we provide an in-depth analysis of studies reporting increased CV risk with TTh. Many of the studies were not well-designed, randomized, double-blind, prospective clinical trials but rather post hoc analyses of cohort data. These studies may reflect bias in how treatment and nontreatment decisions are made or reflect conclusions based on widely cited methodological flaws.

Conclusion: Appropriate patient selection supported by low pre-treatment T levels and monitoring T levels during treatment with the goal of achieving and maintaining physiologic levels all contribute to the safe and effective use of TTh in men with AOH. **Khera M, Miner M, Jaffe J, et al. Testosterone Therapy and Cardiovascular Risk: A Critical Analysis of Studies Reporting Increased Risk. J Sex med 2021;18:83–98.**

Key Words: adult-onset hypogonadism; cardiovascular disease; testosterone; testosterone therapy

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[1]Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA;

[2]Clinical Professor of Family Medicine and Urology, Brown University, Providence, RI, USA;

[3]Antares Pharma, Inc, Ewing, NJ, USA;

[4]Division of Urology, Department of Surgery, University of Utah School of Medicine, Salt Lake City, UT, USA

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INTRODUCTION

In 2015, an expert panel assembled by the Sexual Medicine Society of North America (SMSNA) convened to discuss how to diagnose and treat men with "adult-onset hypogonadism" (AOH), a clinical and biochemical syndrome that is a clinically distinct testosterone deficiency (TD) and may be accompanied by signs and symptoms commonly associated with both testicular and hypothalamic-pituitary dysfunction (Table 1).[1] This syndrome has elements of both primary and secondary

hypogonadism, with many men presenting with inadequate pituitary response to low testosterone (T) levels.[1] Although testosterone (T) levels decline as men age, AOH is not exclusively characterized by an "age-related" TD; rather, it can occur in men who may have common comorbidities associated with aging.[2,3] Established risk factors for development of AOH include cardiovascular disease (CVD), obesity, type 2 diabetes, chronic obstructive pulmonary disease, HIV infection, obstructive sleep apnea and/or sleep disorders, chronic opioid use, and corticosteroid use.[1,4]

Treatment of AOH often involves lifestyle modifications such as weight loss and improved diet, exercise, and sleep, together with exogenous T therapy (TTh). TTh is used for the treatment of TD, with the goal of restoring T concentrations to within the physiological range (~300−1,100 ng/dL), often alleviating TD-related signs and symptoms.[5,6] Guidelines from various societies for the diagnosis and treatment of TD are listed in Appendix 1.[6−10] Today, many Food and Drug Administration (FDA)-approved TTh are available to restore serum T levels within the normal physiological range, each formulation associated with a unique efficacy and adverse event (AE) profile. In addition, there are differences in dose, pharmacokinetics, and method of administration (Table 2).[11−28] Benefits of TTh include improvements in sexual function,[29−31] increased muscle mass and decreased fat mass[32,33]; effects on physical performance[30,34] and energy levels are more varied.[31,35] However, based on potential TTh misuse, the FDA limited the indications for TTh to classical primary and secondary hypogonadism, and not for AOH.[36,37] Specifically, the FDA concluded that the available evidence does not support an indication for TTh for "age-related hypogonadism," placing those physicians who treat men with AOH in the predicament of prescribing T off-label.

Although TTh has been in clinical use for nearly a century, prior to 2013, few publications supported an increased CV risk in patients treated with TTh; in fact, most showed beneficial CV effects of TTh and that low T levels were generally associated with an increased risk of atherosclerosis, CV risk factors, and mortality.[38,39] Since 2013, published studies have contradicted this body of literature, contributing to ongoing debates in the medical community regarding the effects of TTh on cardiovascular health.[40−43]

As the literature is replete with studies demonstrating beneficial impacts of TTh on CV and overall health, we limited our review to the literature supportive of negative effects of TTh on CVD and summarize the available data on the putative mechanisms underlying increased CV risk. We also address the impact of both the current FDA perspective and various professional society guidelines on the use of TTh for treatment of AOH on clinical practice.

METHODS

A search was conducted in PubMed for studies reporting an association between TTh and increased CV risk. Key search terms included "testosterone therapy" and "cardiovascular health," "coronary heart disease," "testosterone therapy," and "hypogonadism." Redundant or irrelevant articles were eliminated; additional references from published studies were reviewed for relevant material. We critically evaluated the studies that promoted the controversy surrounding TTh and increased risk, as well as additional clinical studies, large, population- or community-based studies, systematic reviews, and meta-analyses refuting those findings. An analysis of the literature was performed for clinical and laboratory findings related to the putative mechanisms underlying increased CV risks: upregulation of erythropoiesis, increased T:estradiol (E_2) ratios, increased human platelet thromboxane A_2 (TXA_2) levels, and insufficient T repletion.

Table 1. Clinical signs, symptoms, and conditions consistent with adult-onset hypogonadism and low testosterone levels[1]

Most specific signs/symptoms	More general signs/symptoms	Conditions commonly associated with low testosterone level and adult-onset hypogonadism
Reduced sexual desire and activity	Decreased energy, motivation, initiative	Type 2 diabetes
Decreased spontaneous erections	Delayed ejaculation	Metabolic syndrome
Erectile dysfunction	Reduced muscle bulk and strength	Chronic obstructive lung disease, obstructive sleep apnea syndrome
Hot flushes/sweats	Diminished physical or work performance	End-stage renal disease, hemodialysis
Decreased testicle size	Mild anemia (normocytic, normochromic)	Osteoporosis
Loss of pubic hair, reduced shaving requirement	Depressed mood, irritability	HIV-associated weight loss
Increased body mass index, visceral obesity	Poor concentration and memory	History of infertility, cryptorchidism, pituitary disease, delayed puberty
Height loss, low trauma fractures, reduced bone mineral density	Sleep disturbances, sleepiness	Treatment with opioids or glucocorticoids

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Table 2. Currently available testosterone therapies[11,12]

Formulation	Drug	Common dose	Dosing frequency	Pros and cons
IM injection	Testosterone enanthate[14]	50-400 mg	Every 2-4 weeks	Pros: • Relatively inexpensive • Relatively infrequent dosing Cons: • IM injection and office visit required • Peaks and troughs in T levels • Potential for IM injection site pain
	Testosterone cypionate[15]	50-400 mg	Every 2-4 weeks	Pros: • Relatively inexpensive • Relatively infrequent dosing Cons: • IM injection and office visit required • Peaks and troughs in T levels • Potential for IM injection site pain
	Testosterone undecanoate[16]	750 mg	Every 4 weeks, then every 10 weeks thereafter	Pros: • Infrequent dosing Cons: • Relatively expensive • Part of REMS program due to association with POME and anaphylaxis • Potential for injection site pain
Nasal	Intranasal T gel[17]	1 actuation in each nostril (11 mg)	3 times/day	Pros: • Noninvasive • Self-administered • Lower risk of transfer to partner or child Cons: • Frequent dosing • Risk of nasal irritation
Buccal	Mucoadhesive T buccal system[18]	30 mg tablet	2 times/day	Pros: • Noninvasive • Dosing mimics daily rise/fall of T Cons: • May be difficult to keep in place • Risk of gum-related AEs
Subdermal	Subdermal T pellet implantation[19]	150-450 mg	Every 3-6 months	Pros: • Infrequent dosing Cons: • Requires local anesthesia and surgical implantation • Risk of infection/AE at implant site • Risk of extrusion through the skin
Transdermal	Transdermal T patch[20]	4 mg	Once/day	Pros: • Noninvasive • Self-administered Cons: • Risk of AE skin reactions (pruritus, blistering)
	T gels and solutions[21–26]	40-60 mg	Once/day	Pros: • Noninvasive • Self-administered Cons: • Risk of transfer to others

(continued)

Table 2. Continued

Formulation	Drug	Common dose	Dosing frequency	Pros and cons
Subcutaneous injection	Testosterone enanthate[27]	75 mg	Weekly	Pros: • Auto-injector produces accurate and rapid dosing • Self-administered • Virtually pain free administration • Weekly dosing Cons: • Occasional bruising, redness, or bleeding
Oral capsules	Testosterone undecanoate[28]	237 mg	Twice daily	Pros: • Self-administered Cons: • Twice daily dosing • Recommended to take with food; food affects absorption

AE = adverse event; IM = intramuscular; POME = pulmonary oil embolism; REMS = Risk Evaluation and Mitigation Strategy; T = testosterone.

RESULTS

Critical Evaluation of Studies Supporting Increased CV Risk Associated with TTh

Prior to 2013, few studies spanning multiple decades supported an increase in CV risk in patients treated with TTh; in fact, most studies showed beneficial CV effects of TTh. However, in the past decade, some published retrospective studies of healthcare and prescription databases have suggested that there is an increased risk of CV events in men receiving TTh. In a study of 8,709 men who had undergone coronary angiography and had serum TT levels <300 ng/dL, an adjusted analysis showed that a higher overall rate of myocardial infarction (MI), stroke, and death was reported among 1,223 men receiving TTh, compared with men who did not receive TTh.[40] However, errors in data collection and analysis resulted in multiple published errata, and the use of an unvalidated statistical methodology and misreporting of results were flagged by physicians, scientists, and medical societies, ultimately resulting in a petition for retraction from the *Journal of the American Medical Association* based on lack of credibility. In its response to a Citizen's Petition, the FDA was forced to concede that "given the described limitations of the study by Vigen et al, it is difficult to attribute the reported findings to testosterone treatment."[44] These data, as collected prior to editing, reweighting, and analysis, showed a lower rate of AEs among men receiving TTh than men who did not, consistent with results of 2 prior studies that reported the mortality rate was cut in half in among men receiving TTh compared with untreated men.[45,46]

Retrospective studies by Finkle et al,[41] Layton et al,[47] and Loo et al[48] used information from health insurance databases to retrospectively study CV events following TTh. However, claims databases represent a weak tool to investigate CV risk. Finkle et al[41] reported nonfatal MI rates in the 90 days after a T prescription compared to the previous 12 months, using nonfatal MI diagnosis codes. Additionally, the comparator arm was comprised of men prescribed a phosphodiesterase type 5 inhibitor rather than untreated men, thus biasing results. Similar to the study by Vigen et al, the FDA conceded the difficulty in using the results from the study by Finkle et al to attribute an increased risk of nonfatal MI to T use alone.[44] Layton et al compared the CV safety of T injections, patches, and gels in men newly initiating TTh following a 180-day washout period using administrations claims from 2 databases in the United States and one database from the United Kingdom from 2000 to 2012.[47] The authors reported only a slight increase in MI and a very small absolute incidence of an increased risk of outcomes in new T injection initiators compared with gels. Owing to the inherent limitations in the use of secondary health-care data, outcomes could not be consistently compared across all databases and the lack of important patient characteristics and laboratory results posed as additional confounders of assessment. In the study by Loo et al, men aged ≥45 years with low T diagnosis who had experienced ischemic stroke/transient ischemic attack (TIA)/MI were evaluated.[48] Results showed an increased risk in composite CV outcomes (ischemic stroke/TIA/MI) with continuous T treatment compared to nonusers, especially within the first 2 years. Furthermore, the risk of all-cause mortality was significantly lower with TTh users compared with TTh nonusers.

Wallis et al conducted a retrospective, population-based, matched cohort study of men ≥66 years old newly treated with TTh and controls matched for age, region of residence, and comorbidities.[49] The primary objective was to assess the effect of long-term TTh exposure on mortality. Secondary outcomes included composite CV events (MI, stroke, or venous thromboembolic event) and prostate cancer diagnosis. The study included 10,311 men treated with TTh and 28,029 untreated men over a median follow-up of 5.3 years and 5.1 years, respectively. The authors reported that patients in the lowest tertile of T exposure had increased risk of mortality (hazard ratio [HR] 1.1, 95% CI 1.03-1.20) and CV events such as MI or stroke (HR 1.26, 95% CI 1.09-1.46) compared with controls.

However, their study also reported that compared with matched controls, shorter duration (median 2 months) of TTh was associated with increased mortality and CV risk, whereas long-term TTh use (median 35 months) was associated with a reduction in mortality and CV risk.

The Testosterone in Older Men with Mobility Limitations (TOM) study by Basaria et al evaluated the safety and efficacy of TTh in subjects enrolled in a prospective randomized trial designed to determine the effects of T exposure on lower-extremity strength and physical function in older men.[42] In this study, 209 community-dwelling men ≥65 years of age with limitations in mobility and a total serum T level of 100-350 ng/dL or a free T level of <50 ng/dL were randomly assigned to receive T gel or placebo gel to be applied daily for 6 months. At baseline, there was a high prevalence of hypertension, diabetes, hyperlipidemia, and obesity, and a greater proportion of men in the TTh group reported they had received a diagnosis of hyperlipidemia or were taking a statin. The study did find benefit for muscular and functional responses with TTh vs placebo, but the trial was stopped early because of increased CV AEs in the treatment arm (23 in the TTh group vs 5 in the placebo group). Of the 23 CV events reported in the TTh group, only 4 were considered major adverse cardiac events (MACEs; 1 death, 2 MIs, and 1 stroke). The main limitations in this study relate to the small sample size, the small number of AEs reported in the study, and the fact that the trial was not designed nor adequately powered to investigate CV event rates.[39] In addition, there were significant limitations with respect to confirming the reported CV AEs: most were incidentally noted, subjective, or of questionable clinical importance, particularly because the enrolled population included only frail elderly men. The authors even conceded that "the lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the 2 trial groups may have been due to chance alone." It has also been suggested, based on subsequent analysis, that the AEs reported in this study were associated with higher serum T concentrations that may have resulted from use of higher than recommended T doses or combining this with strenuous exercise.[39]

Onasanya et al[50] assessed published systematic reviews for evidence of an association between TTh and CV events and found that data from 7 systematic reviews of randomized controlled trials suggest a small increase in CV risk associated with TTh. Of the 7 studies that met their criteria, 6 demonstrated that TTh did not increase CV risk,[51–56] and one study reported that TTh was associated with increased CV events, especially in men over 65 years old, especially during the first year of use.[56] A meta-analysis by Xu et al of 27 placebo-controlled T studies of 12-week duration or longer showed an association.[43] As with all meta-analyses, the validity of the results and conclusions are based heavily on the quality of the studies selected for inclusion.[39] In this case: (i) only studies in which one or more CV events were reported were included, so studies with no CV events were not included, exaggerating the apparent rate of events; (ii) 2 of the 27 studies contributed 35% of all CV events in the T arm, one as discussed in the TOM study above and the other was a study conducted in Copenhagen and published in 1986 that evaluated an oral formulation of micronized T administered at much higher than approved T doses in liver disease[42,57]; and (iii) not many of the AEs categorized by Xu et al as CV in nature would reasonably be considered as such. Interestingly, without the contribution of Basaria et al and the Copenhagen study, the rates of CV AEs were similar in the T (78/1,599 men [4.9%]) and placebo groups (60/1,174 men [5.1%]). Notably, meta-analyses published both prior to and since the study conducted by Xu et al did not support the conclusion that exogenous T therapy increases the risk of a CV events.[50,52]

An extensive review reanalyzed the studies cited by the FDA as evidence of increased CV risk with the intent of minimizing the methodological flaws of the studies.[39] The authors conclude that at the appropriate dose, TTh is not associated with an increase in CV risk and may even be associated with a decreased risk.[39] In support of this, several additional studies published since are consistent with the conclusion that there is a lack of association between TTh and CV risk.[45,52,58–66]

No Association Found Between TTh and an Increase in CV Risk

In 2014, Baillargeon et al evaluated U.S. Medicare recipients aged 65 years and older from a large (N = 25,420) database: 6,355 men treated with ≥1 injection of T between 1997 and 2005 were matched 1:3 with 19,065 T nonusers on the basis of a composite MI prognostic score.[59] A significant trend toward reduced MI rates with T use was noted. For men considered to have the highest composite prognostic MI risk score (based on 30 covariates measured during the 12 months before T initiation/index date), treatment with TTh was associated with significantly reduced MI risk (HR 0.69; 95% CI 0.53-0.92). Moreover, a dose-response analysis indicated that the risk of MI did not increase with an estimated cumulative T dose. In 2017, Cheetham et al performed a retrospective comparison of over 8,800 men with TD prescribed T and over 35,500 who were never dispensed T.[60] In this study, the primary outcome was a composite of MACE endpoints, including MI, coronary revascularization, unstable angina, stroke, TIA, and sudden cardiac death. The rate of the MACE was lower in the TTh group (16.9 per 1,000 person-years) compared with men who were never prescribed T (23.9 per 1,000 person-years). More recently, a retrospective analysis of 14 prescription databases found that TTh was not associated with increased thrombosis, MI, stroke, composite CV events, or mortality.[67]

The T Trials were a group of coordinated, double-blind, multicenter, placebo-controlled clinical trials designed to determine whether TTh is beneficial in older men with low T levels and evidence of impaired mobility and/or diminished libido and/

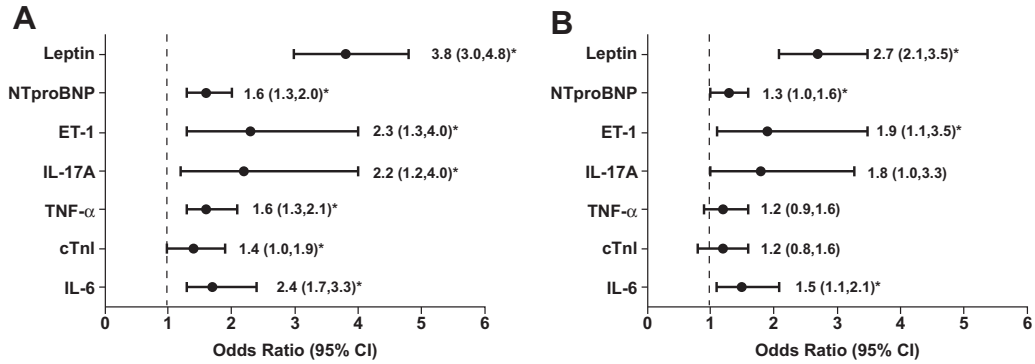

Figure 1. Relationship between low testosterone levels and increased cardiovascular risk.[127] Panel A shows the cardiovascular risk adjusted for age and BMI. Panel B show the cardiovascular risk adjusted for age, BMI, HbA_{1c}, high-sensitivity C-reactive protein, and high-density lipoprotein. *Testosterone levels <250 ng/dL associated increased likelihood of elevated levels. BMI = body mass index. Figure reprinted with permission from Pastuszak AW, et al J Sex Med 2017;14:1,095-1,103.

or reduced vitality.[29] Pooled assessments of AEs from all 7 studies comprising the T Trials revealed that there were no significant differences in CV events between the TTh and placebo groups during the first year of TTh.[29] The individual clinical trials of the T Trials were each designed to study a potential improvement in a different facet of TD: improving mobility (Physical Function Trial), sexual function (Sexual Function Trial), fatigue (Vitality Trial), cognitive function (Cognitive Function Trial), hemoglobin (Anemia Trial), bone density (Bone Trial), or coronary artery plaque volume (CV Trial). The CV Trial enrolled 170 men aged 65 years or older with symptomatic hypogonadism (88 assigned to TTh; 82 to placebo).[68] The results, published in 2017 by Budoff et al, showed a significantly greater increase in noncalcified plaque volume (measured by coronary computed tomographic angiography [CCTA]) from baseline to 12 months in the TTh vs placebo groups.[68] These authors suggest at least 2 limitations to their study that relate to the use of noncalcified plaque volume based on CCTA as the CV endpoint: first, assumptions about plaque composition at CCTA were not confirmed pathologically, and second, radiologic characteristics of coronary artery plaques are only surrogate outcomes, and they do not necessarily correlate with the frequency or extent of plaque rupture or thrombosis.[68] Calcified plaque volume, on the other hand, did not increase. The clinical significance of this increase in noncalcified plaque volume is unknown. The authors concluded that larger and longer-term clinical trials are necessary to evaluate clinical CV events.

Putative Mechanisms Underlying CV Risk

T-Induced Erythrocytosis

Erythrocytosis, generally defined as a hemoglobin (Hb) level higher than 18.5 g/dL or hematocrit (Hct) ≥52%, is the most common dose-limiting adverse effect of TTh.[69,70] TTh is frequently associated with elevations in both Hb and Hct.[51,54,71,72] The mechanism by which T induces erythrocytosis is believed to involve erythropoietin stimulation[73] and suppression of hepcidin.[74] Recent findings also suggest a possible role for serum dihydrotestosterone, a potent metabolite of T, in the development T-induced erythrocytosis.[75] An increased Hct has long been known to be associated with increased blood viscosity,[76–78] and it is this hyperviscosity that is one hypothesis to denote an increased risk for thromboembolic events and ischemic sequela.[1,79–81]

Rates of T-induced erythrocytosis seem dependent upon both T dose and T serum level, with higher T doses and levels associated with greater rates of erythrocytosis.[82–84] In addition, certain T formulations seem to be more likely to induce erythrocytosis than others.[82,84–86] A measurement of Hct >50% is significantly ($P < .0001$) more common with T injections (66.7%) than with T gels (12.8%) or pellets (35.1%).[87,88] However, it may be the dose or the pharmacokinetic (PK) profile of the formulation, rather than the actual route of administration, that has a greater influence on erythrocytosis[72,84]: use of short-acting injectable T preparations is more commonly associated with serum T fluctuations and supraphysiologic T levels.[86,88,89] In contrast, longer-acting preparations (eg, extended-release intramuscular (IM) injections, subcutaneous injections, T implants) that do not cause prolonged supraphysiologic levels tend to be associated with a lower incidence of erythrocytosis.[82,90–92] Specifically, extended-release injections of testosterone undecanoate (TU) are associated with a rate of erythrocytosis of approximately 7%.[93]

In terms of CV risks associated with T-induced erythrocytosis, prospective, randomized, controlled trials have failed to detect a direct relationship between T-induced erythrocytosis and subsequent risk for CV events (including stroke and deep vein thrombosis).[94–98] However, as proposed by Kloner et al, a large, prospective, randomized, placebo-controlled, double-blinded, long-term study with a clearly defined objective of evaluating the effect of TTh on MACE in men with verified symptomatic hypogonadism of at least 1 year is needed to assess the effect of TTh on CV safety.[99] The currently ongoing TRAVERSE study (ClinicalTrials.gov Identifier: NCT03518034), is a blinded, placebo-controlled

Table 3. Studies showing relationship between low endogenous testosterone and increased cardiovascular risk and mortality

Author (Year)	Study population	Study design	Primary findings
Hak et al (2002)[123]	1,032 nonsmoking men (n = 504) and women (n = 528); mean age was 67.9 years (men) and 69.5 years (women)	Population-based, prospective cohort study (Rotterdam Study)	Low levels of T increases the risk of severe aortic atherosclerosis and progression of aortic atherosclerosis in elderly men
Khaw et al (2007)[124]	11,606 men 40–79 years old surveyed in 1993–1997 and followed up to 2003	Prospective population study (European Prospective Investigation into Cancer in Norfolk); nested case-control study	Low endogenous T concentrations associated with all-cause (n = 825) and CV (n = 369) mortality
Laughlin et al (2008)[125]	794 men, 50–91 years old	Population-based study	Low TT associated with higher all-cause mortality (HR 1.4; 95% 1.14–1.71) and CV mortality (HR 1.38; 95% CI 1.02–1.85)
Araujo et al (2011)[126]	11 studies for all-cause mortality (n = 16,184 men) 7 studies of CV mortality (n = 11,831 men)	Systematic review and meta-analysis	Low TT associated with increased risk of all-cause and CV mortality
Ohlsson et al (2011)[157]	2,416 men, 69–81 years old over median 5-year follow-up	Prospective population-based MrOS (Osteoporotic Fractures in Men) Sweden study	Higher TT levels associated with lower risk of CV events (HR 0.70, 95% CI 0.56–0.88) in elderly men
Muraleedharan et al (2013)[46]	581 men with type 2 diabetes, 31–88 years old, followed up over a mean period of 5.8 years	Prospective follow-up study	Low TT levels were associated with higher all-cause mortality (HR 2.02; 95% CI 1.2–3.4) in multivariate-adjusted model among men with type 2 diabetes mellitus
Soisson et al (2013)[129]	Case-cohort design included 495 randomly selected sample of men (>65 years) and incident cases of CV event after 4 year follow-up	Data from French Three-City prospective cohort study	Increased risk of coronary disease or stroke among elderly men with TT levels in the lowest (HR 2.23; 95% CI 1.02–4.88) and highest (HR 3.61; 95% CI 1.55–8.45) quintiles
Yeap et al (2014)[158]	3,690 men 70–89 years old at baseline	Population-based cohort study of community-dwelling men (Health in Men Study [HIMS])	Higher TT levels were associated with lower incidence of stroke (HR 0.56; 95% CI 0.39–0.81) but not MI in men with higher TT levels

CV = cardiovascular; HR = hazard ratio; T = testosterone; TT = total testosterone.

study that began recruiting patients in 2018 with a target enrollment of 6,000 patients and aims to investigate the effect of topical TTh on MACE in symptomatic men with TD.[61] The results from this study are forthcoming. The current Endocrine Society Clinical Practice and American Urology Association guidelines state that Hct values > 54% warrant discontinuation of TTh or therapeutic phlebotomy and consideration of dose reduction.[6,100] In addition, if Hct levels become markedly elevated, phlebotomy should be considered for expedited normalization of levels.

Estradiol

E_2 has a variety of physiological functions in men, including effects on brain, cartilage, and bone, as well as on CV health.[101–103] Abnormal increases in E_2 can lead to mood swings, breast tissue changes, and fluid retention. Most (~80%) of the circulating E_2 in men is derived from aromatization of circulating T.[104,105] In men with TD, E_2 concentrations are also low, and during TTh, E_2 tends to increase when serum T increases, largely maintaining the T:E_2 ratio.[106] However,

imbalances in this ratio in either direction (ie, higher or lower T:E_2 ratios) could be harmful, potentially promoting the development of heart disease and increasing the risk of cerebrovascular disease.[107,108] One study has reported in older, obese men receiving IM T injections, a higher rate of whole body T aromatization, possibly due to the higher fat mass in older men.[106] However, another study showing no correlation between age and body mass index with E_2 levels or has not confirmed this[87] so at the current time it is unclear whether fat mass plays a role in influencing T:E_2 ratios and whether increasing aromatization of T to E_2 has any role of increasing CV risk.

Human Platelet Thromboxane A_2

Although the mechanism is not well understood, *in vitro* studies suggest that one potentially prothrombotic influence of T is the upregulation of platelet TXA_2 receptors. The function of human TXA_2 is to assist in platelet aggregation and vascular smooth muscle contraction,[109,110] and increased platelet aggregation potentially promotes atherogenesis/thrombosis.[111] During numerous thrombotic CV events, including unstable angina, the synthesis of TXA_2 is increased.[112] However, there is no direct evidence for an association between TXA_2 receptor density and CV risk in humans,[111,113] nor is there evidence that a T-induced TXA_2 increase induces increased CV risk.

Blood Pressure

Animal studies have shown that T and its metabolites play a significant role in BP control and deficiency may contribute to the pathogenesis of hypertension.[114] The antihypertensive effects of androgens may be mediated by blocking L-type voltage-gated calcium channels and, to a lesser extent, by blocking multiple signaling pathways operating during α-adrenoreceptor-induced vasoconstriction.[115] These findings demonstrate that hypotestosteronemia may be a risk factor for hypertension.[114] Plasma concentrations of natriuretic peptides (NPs) are elevated in heart failure, and these peptides are considered to play a compensatory role for heart failure due to their diuretic, natriuretic, and vasodilating actions.[116] Higher levels of N-terminal pro-B-type NP (NT-proBNP) have been reported in hypertensive patients, and a strong association between circulating cardiac NPs and CV risk has been reported in a systematic review and meta-analysis of 40 prospective studies.[117,118] Recently, a study reported the negative effect of T on the cardiac NP system. Healthy men (n = 202) aged 20 to 50 years were treated with goserelin acetate to suppress endogenous T and estradiol production and anastrazole to prevent the aromatization of T to estradiol and were then randomly assigned to 5 different doses of topical T gel. The authors report that suppressing T production in men increased circulating NP levels, which decreased following 12 weeks of T gel treatment, but also offer that higher T levels may only partly explain why men have lower NP levels compared with women.[119] However, in a randomized, double-blind, placebo-controlled trial of hypogonadal men with heart failure, treatment with 5 mg transdermal T patch did not result in any significant change in serum BNP levels.[120] The exact mechanism for T-induced BP reduction has not been completely elucidated.

Insufficient Repletion of Serum T Levels

One hypothesis for the association between TTh and CV risk that is sometimes seen in clinical studies is that when physiological T levels are not achieved using TTh, either because of T underdosing or overdosing, CV risks may increase. Since we know that low endogenous T levels are associated with increased CV risk, it is reasonable that TTh with less-than-adequate efficacy or poor compliance that fails to raise serum T levels to >300 ng/dL would be associated with, but not necessarily causative of, an increased CV risk relative to a population with serum T levels in the physiological range.[121–126] Recently, a large (N = 10,041 men) database study examined the association of circulating T levels with a panel of 10 high-sensitivity CV risk biomarkers (including cardiac troponin I, endothelin-1, interleukin-6, tumor necrosis factor-α, interleukin-17A, NT-proBNP, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, Hb A1c, and leptin).[127] An inverse relationship between plasma T levels and CV risk was observed for 9 of the 10 CV markers (Figure 1[127]).

Conversely, the effects of supraphysiologic serum T levels (>1,100 ng/dL) on CV risk have been less studied, since it is not a goal of TTh to raise T levels above the upper limit of the normal physiological range. In general, lower circulating T levels predict higher CVD-related mortality. However, it is possible that a U-shaped association exists between circulating androgens and CV events or mortality outcomes, where serum T at very low or very high levels may be associated with an increase in CV risk.[128] In the TOM trial, men with the highest quartile T levels (512-1957 ng/dL) had an increased risk for unconfirmed CV events (HR: 2.4; $P = .05$) compared with all other subjects in the study.[42] Similarly, an analysis of 495 men taken from the larger French Three-City prospective cohort study found a J-shaped association between plasma T and ischemic arterial disease in men 65 years and older.[129] The HR associated with the lowest and the highest T quintiles relative to the second quintile were 2.23 and 3.61, respectively ($P < .01$). Additional analysis for coronary heart disease showed similar results (HR: 3.11 and 4.75). This J-shaped association was also observed between bioavailable T and ischemic arterial disease risk.[129] These studies are observational and do not prove causality; randomized controlled trials are needed to fully clarify the effects of T on CV risk in men.

There are known differences in serum T levels because of the use of different types of T formulations. Specifically, compared with patches and gels, IM injections of T dosed on an infrequent basis are associated with serum T peaks and troughs that cause supraphysiologic levels soon after the injections and before the T levels drop back down into the physiological range.[47,86,130,131] In contrast, a weekly subcutaneous, autoinjectable T formulation

received FDA approval in 2018 and is able to achieve a more stable PK profile resulting in less fluctuation in serum T levels.[132,133]

The effect of normalizing T levels on the incidence of MI and mortality in 83,010 male veterans with documented low TT levels has recently been investigated.[134] The participants were divided into 3 groups: those with normal T levels (defined as within the reported laboratory reference range) after TTh; those that did not achieve normal T levels after TTh; and those that did not receive TTh. The authors found that those in the normalized TTh group had a significantly lower risk of MI and mortality compared to the other 2 groups and that there was no significant difference between the groups that did not achieve T normalization and those that received no TTh. These same authors found a similar reduction in the risk of atrial fibrillation with T normalization.[135] However, these results were from a nonrandomized, observational study limiting the interpretation of results.

Another confounding metric present in the various CV risk trials is the duration of exposure. Much of the evidence for an increase in CV risk with TTh is derived from studies with short treatment duration and follow-up. As demonstrated in the study by Wallis et al, over a 5-year period, cumulative TTh was associated with a reduced risk of mortality and CV events but risks were increased in men with a shorter duration of therapy.[49] Martinez et al found that TTh is associated with an increased risk in venous thromboembolism, but that this risk peaks rapidly in the first 3 months after treatment initiation and declines gradually thereafter.[136] These results suggest that not only are randomized, controlled, clinical trials necessary, but that they must also be of sufficiently long duration to clearly evaluate CV risk. In their overview of systematic reviews and meta-analyses evaluating the association between TTh and CV events, Onasanya et al concluded that "any randomized clinical trial aiming to detect a true difference in CV risk between treatment groups receiving exogenous T and their controls (with a 2-sided *P*-value of 0.05 and a power of 80%) would require at least 17,664 participants in each trial group" and would require clinical trials to extend for long durations approaching a decade.[50]

DISCUSSION

Perspectives on the Current Status of the Literature on CV Risk With Respect to TD and TTh

A large body of data supports an increased risk of atherosclerotic cardiovascular disease (ASCVD) events (eg, MI, stroke) and mortality in individuals with low endogenous T levels, including studies of community populations, as well as patient populations with a variety of medical conditions, including androgen deprivation and diabetes (Table 3). Specifically, studies show that low T levels are associated with a number of ASCVD contributory factors, including atherosclerosis progression, production of proinflammatory cytokines, increases in arterial thickness/stiffness,[137] and increases in total cholesterol and low-density lipoprotein.[121,122] Hak et al found an independent inverse association between T levels and severity of aortic atherosclerosis in over 1,000 men 55 years of age and older.[123] In a larger, longer-term, prospective study (11,606 men; ages 40 to 79; study duration 10 years), Khaw et al found that endogenous T concentrations were inversely related to CV and all-cause mortality.[124] Similarly, in another long-term, population-based study, Laughlin et al found an association between TD and an increased risk of death in men followed up over 20 years, independent of multiple risk factors and pre-existing health conditions.[125] In a systematic review of 21 community-based studies of men, including a meta-analysis of 12 studies, Araujo et al found that low endogenous T levels are associated with both all-cause and CV mortality.[126]

Indirect support for this inverse relationship between T levels and CV risk comes from a meta-analysis showing an association between androgen deprivation therapy and an increased risk of CV events and mortality.[138] More recently, in a meta-analysis of 37 prospective observational studies, low T was shown to predict CV morbidity and mortality.[139] Another study showed that in 3,443 men at least 70 years of age, those with the highest serum T levels were found to have the lowest mortality, while men with the lowest T levels had the highest mortality.[140] Some consider the evidence for an inverse relationship between T levels and CV risk strong enough that low T levels can be considered a biomarker to predict increased CVD risk.[141]

TD commonly presents alongside endemic metabolic risk factors for ASCVD, such as diabetes, dyslipidemia, hypertension, and obesity. Support for the relationship between TD and CVD risk factors comes from observational studies that show an association between low T levels and high blood pressure (BP)[142] and left ventricular hypertrophy.[143] A cross-sectional study of 1,098 adult Korean men, including 139 monozygotic twin pairs, showed that total T was inversely associated with abdominal obesity, high-density lipoprotein cholesterol, and high BP, and free T was inversely associated with abdominal obesity and high BP.[144] Further evidence for the relationship between T and central systolic BP comes from a study that demonstrated that 12 weeks of dietary modification and aerobic exercise training increased previously low serum T levels and decreased previously high central systolic BP in overweight and obese men.[145] Similarly, multiple reports of the benefits of TTh with TU from a large database of elderly men showed an association with dietary intervention and exercise on metabolic parameters in men with TD, with long-term improvements in obesity and waist circumference and downstream benefits to lipid profile, inflammation, glycemic control, and BP.[146–150] Recently, a long-term study with up to 12 years of follow-up showed improvements in cardiometabolic function and reduced CV risk in men with TD treated with TU.[65,151] In an interim analysis with a median follow-up of 7 years, men receiving TU (n = 360) reported significant reductions in blood glucose, systolic and diastolic

blood pressure, liver enzymes, lipid profiles, weight, waist circumference, and body mass index compared with untreated controls (n = 296); there were also no CV-related deaths in the TU group and 19 in the untreated group.[151] The effects of TTh on metabolic factors among hypogonadal men with metabolic syndrome showed significant differences in waist circumference, body fat percentage, fasting plasma glucose, triglycerides, and hemoglobin A_{1c} (HbA_{1c}) levels after 12 months of IM therapy.[152] Collectively, these studies spanning multiple decades showed an improvement in CV effects in men treated with TTh and did not support an association between TTh and an increase in CV risk.

In this review, most of the studies have limitations of cross-sectional data, though some are randomized controlled trials. Here, we have provided an in-depth review of the methodological flaws of each trial. Despite our best attempts to be inclusive in our examination of those studies critical of TTh and supportive of increased CV risk, the choice of these individual studies may reflect the individual and collective bias of the authors.

FDA Recommendations and Societal Guidelines for Use of TTh for Treatment of TD: Impact on Clinical Practice

The current FDA perspective is that TTh should be limited to men with an identified underlying etiology for TD, that is, classical primary or secondary hypogonadism caused by specific well-recognized medical conditions. According to the FDA, secondary hypogonadism associated with older men and chronic disease states, is not an indication for TTh, regardless of whether these men are symptomatic of TD. In addition, the FDA mandates that the T product label include language noting that T products may be associated with increased risk of CVD.[153] However, several medical professional societies do not agree with this stance. The American Urological Association, in their position statement on TTh, state that it cannot be definitively determined whether TTh increases or decreases the risk of CV events, such as MI, stroke, CV-related death, and all-cause mortality. Moreover, the 2018 AUA Testosterone Guidelines state that patients should be informed that there is no definitive evidence linking TTh to a higher incidence of CVD or venothrombolic events.[154] The Sexual Medicine Society of North America also states that current evidence does not support the assertion that T therapy increases the risk of heart attacks, stroke, or other CV risks.[155] Guidelines from The Endocrine Society suggest no definitive association between T supplementation and increased CV risk or venous thromboembolic events in men with TD and that more adequately powered randomized trials are needed.[100]

CONCLUSIONS

In summary, upon critical examination of the literature purported to support an increase in CV risk with TTh, we did not find definitive evidence to support that TTh increases CV risk. To date, there have not been large, long-term, placebo-controlled studies examining the risk or safety of TTh on CV outcomes. However, there is overwhelming evidence spanning multiple decades from numerous researchers whose studies show an improvement of CV risk factors in response to TTh in men with AOH. When prescribing TTh, it is important to consider appropriate patient selection and patients' CV risk factors, obtain pretreatment T levels, select a formulation that allows for patient compliance, and monitor for potential TTh-related AEs. T levels of men receiving TTh must be monitored to ensure physiological T levels are achieved and maintained to benefit patients' overall health as well as CV outcomes and per major guidelines, to ameliorate TD signs and symptoms.

So how can we reconcile these differing perspectives on patient management? What are the key considerations for T prescribers? Clearly, the benefits from TTh afforded to men with idiopathic and/or AOH are an important consideration. However, given the restrictions of the new FDA indications, a large majority of such men are being treated with TTh off-label.[156] Further research aimed at clarifying the relationship between TTh and CV risks should be aggressively pursued and is currently being examined in the TRAVERSE study. In the meantime, it is important to (i) appreciate the limitations of the evidence that forms the basis for the FDA warnings and (ii) follow guidelines regarding prescreening and monitoring of T levels before and during TTh. In addition, there are differences in the various T formulations with respect to PK and AEs; therefore, it is important to select a formulation that is most appropriate for the patient. Importantly, AEs, including those related to CVD, may be exacerbated by under dosing or fluctuating levels of T.

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Corresponding Author: Mohit Khera, MD, MBA, MPH, Scott Department of Urology, Baylor College of Medicine, 7200 Cambridge St Suite 10B, Houston, TX 77030, USA. Tel: (713) 798-6593; Fax: (713) 798-5553; E-mail: mkhera@bcm.edu

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STATEMENT OF AUTHORSHIP

Mohit Khera: Conceptualization, Methodology, Investigation, Writing — original draft, Writing — review and editing; Martin Miner: Conceptualization, Methodology, Investigation, Writing — original draft, Writing — review and editing; Jonathan Jaffe: Conceptualization, Methodology, Investigation, Writing — original draft, Writing — review and editing, Funding acquisition, Resources, Supervision; Alexander W. Pastuszak: Conceptualization, Methodology, Investigation, Writing — original draft, Writing — review and editing.

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SUPPLEMENTARY DATA

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