REVIEW ARTICLE

Testosterone replacement therapy and cardiovascular disease

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The use of testosterone therapy has a complex history of apprehension and questions regarding its safety. Despite an eventual consensus that testosterone therapy was safe and effective, several studies relating to cardiovascular risks emerged in the last decade, rekindling skepticism regarding the safety of testosterone therapy. Given the utility of testosterone therapy in treating the symptoms of hypogonadism, it remains crucial to closely examine the safety of testosterone therapy. The present article synthesizes the current evidence regarding cardiovascular risks that may be associated with testosterone therapy, the potential mechanisms regarding testosterone's efficacy, and future directions in evaluating the safety of its use.

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INTRODUCTION

Male hypogonadism is a congenital or acquired condition characterized by a deficiency of testosterone (T) and presenting with symptoms of sexual dysfunction, fatigue, loss of lean muscle, and depression [1–3]. Testosterone replacement therapy (TRT) is the hallmark treatment option for men with hypogonadism. After a long history of skepticism, an emerging consensus that TRT was safe and effective was called into question beginning in 2010 after various studies proposed dangerous cardiovascular risks associated with TRT. Since 2010, minimal evidence supports the notion that TRT increases cardiovascular risks. Nevertheless, an FDA label now exists on all T products which warns consumers about ambiguous evidence regarding cardiovascular risks. Given the new modern controversy regarding the safety of TRT, this review will revisit the current landscape of the role of endogenous T in cardiovascular disease, the relationship between TRT and cardiovascular disease, and the potential mechanisms that may explain the physiological effects of T.

METHODS

The PubMed database was searched with no time restriction. The search terms included "hypogonadism" or "testosterone replacement" AND "cardiovascular disease", "metabolic syndrome", "erythrocytosis", "atherosclerosis", "morbidity", and "mortality". Each relevant article was utilized as a source for other published research. All relevant clinical trials since 1977 were evaluated without exclusion criteria. Rather, the strengths and weaknesses of trials are evaluated in the ensuing manuscript.

History of TRT

The current discussion of the safety of TRT is not the first time that use of T has faced skepticism. In 1941, Charles Huggins published a report on a single case of castration in the treatment of prostate cancer and wrote that TRT was assumed to nurture cancerous cells [4]. It wasn't until the late 20th century when studies began to clearly highlight that elevated T did not confer a higher risk for prostate cancer [5, 6], resulting in a subsequent rise in TRT.

Though early concerns arose regarding T and cardiovascular risk, these worries were assuaged by studies demonstrating increased cardiovascular risks associated with low T [7]. However, four studies published between 2010 and 2014 sparked a return of these concerns regarding cardiovascular risks. First, a 2010 study found more cardiovascular events in men treated with topical T than in men treated with placebo. It has since become clear that these documented cardiovascular events included nonspecific changes that are not associated with heart disease and that the experiment included excessively high doses of T, potentially leading to abnormally high serum T levels [8, 9]. Notably, the authors themselves admitted that the differences in adverse events may be statistically meaningless. The FDA effectively ignored the results of the study due to the low overall number of adverse cardiovascular events [10]. In 2013, Vigen et al. published a retrospective study which included 8,507 patients in a Veterans Administration system and found that men with low T who were treated with TRT had higher risks of stroke, myocardial infarction, and death [11]. The authors soon published a correction for misinterpreting their data, which showed that adverse cardiovascular events were actually lower in men treated with TRT. Additionally, the authors explained that about 10% of the study population was women. Various researchers and medical organizations have since called for a retraction of this study [12]. Next, a 2014 study from Finkle et al. displayed higher numbers of myocardial infarctions within 90 days of initiating TRT than in the period prior to treatment initiation. The analysis did not include a control group of untreated men, and TRT was classified as men prescribed T without a confirmation of T consumption [12–14]. Finally, a meta-analysis examining placebo-controlled trials of TRT reported higher rates of adverse cardiovascular events in men given TRT [15]. The FDA later analyzed the data and did not find such an increased risk in adverse cardiovascular events [10]. Interestingly, a broad analysis of studies published over a nearly

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75-year time span found that the four previously mentioned studies were the only studies to suggest an increased cardiovascular risk associated with TRT [8].

In spite of minimal indication of any cardiovascular risk with TRT, the FDA created a new warning in 2015 on all T products, outlining the questionable safety of TRT and limiting the indicated population [16]. The European Medicine's Agency created no such label change on T formulations [17]. In 2018, the Endocrine Society and the American Urological Association published guidelines which indicate that the current evidence does not suggest an elevated cardiovascular risk with TRT, but both reported insufficient data to confidently comment on its overall safety. In addition, both guidelines do not recommend TRT for men with past cardiovascular events. However, there is no indication to halt TRT if patients were utilizing T before the occurrence of a cardiovascular event [18, 19].

Testosterone levels and cardiovascular disease

Several societies have evaluated the guidelines for diagnosis of hypogonadism and the indications for use of TRT in hypogonadal men. The 2018 AUA Testosterone Guidelines state that "The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs" (Moderate Recommendation; Evidence Level: Grade B) [18]. In addition, the 2018 Endocrine Testosterone Guidelines state that "We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated)" (Moderate quality evidence) [19]. Signs and symptoms for both societies include low libido, erectile dysfunction, and fatigue. Finally, the AUA recommends that the target testosterone level be in the middle tertile (450–600 ng/dL) of the normal reference range. (Conditional Recommendation; Grade C) [18]. The Endocrine Society recommends that therapy should aim to raise testosterone levels to the mid normal range [19].

It remains useful to distinguish endogenous levels of T and exogenous provision of TRT and their independent relationship to cardiovascular disease. Overall, findings continually display worse cardiovascular health with lower native serum T levels, with various studies showing a cardioprotective effect with higher serum levels. The Framingham Heart Study analyzed a group of 1251 men aged 55–69 with lower endogenous levels of T and found an increased risk of atrial fibrillation [20]. Similarly, a 2011 meta-analysis of over 22,000 men found increased mortality and overall cardiovascular mortality in men with lower levels of T [21]. One study more specifically reports that men with low levels of T and coronary artery disease had elevated all-cause and cardiovascular mortality rates than men with normal serum T and coronary artery disease [22]. Other studies highlight the potential benefits of higher T levels. A Swedish study of 2416 men found that elevated serum T levels corresponded to a lower risk of adverse cardiovascular events [23]. Interestingly, men in the highest quartile of serum T displayed a reduced risk of abdominal aortic atherosclerosis [24].

More recent data aligns closely with these prior studies. In 2018, a meta-analysis which included 10,479 men reported an association between lower T levels and increased risks of adverse cardiovascular events and cardiovascular mortality over a 6 year follow-up period [25]. Similarly, a 2019 cohort investigation from Denmark evaluated 18,238 men over the course of fifteen years and reported that men lower serum T levels displayed increased 1-year and 5-year risks of myocardial infarction, stroke, venous thromboembolism, and overall mortality even after controlling for comorbidities and patient age [26].

Another subset of studies either show no association between T and cardiovascular health or simply show a more subtle relationship. After two reports from the FINRISK97 study documented an association between low T and diabetes, stroke, and atrial fibrillation [27, 28], a further FINRISK97 study in 2019 followed 7671 individuals with a median follow-up of nearly 14 years and did not find a relationship between low T and cardiovascular disease. Notably, a significant proportion of these individuals were female [29]. Two studies report that men in the lowest and highest ranges of serum T levels display elevated risks of cardiovascular and arterial disease than men in the middle ranges [20, 30], indicating a more complex association whereby T levels sit ideally within a given range.

Diabetes and metabolic syndrome (MetS) – defined by obesity, hyperglycemia, elevated serum triglycerides, and reduced serum high-density lipoprotein – are important predictors of cardiovascular disease [31, 32]. Obesity affects more than one-third of all men in the United States, and some suggest that obesity itself is the number one cause of idiopathic hypogonadism in the developed world [17]. Hypogonadal men in the lowest quartile of serum T have dramatically higher rates of MetS and diabetes compared to men with normal T levels [8]. Two studies from 2019 independently established that low T is a predictor for the development of diabetes and serves a marker for insulin resistance [33, 34]. One randomized controlled trial (RCT) found that TRT enhanced insulin sensitivity in type 2 diabetes or MetS in hypogonadal men [35].

Overall, an overwhelming body of evidence defines low endogenous T levels as a strong predictor of cardiovascular disease and cardiovascular mortality. Conversely, there is no published evidence in recent years displaying higher T levels conferring elevated risks of cardiovascular events and mortality. It remains crucial, however, to keep in mind that population analyses do not imply causality.

TRT and cardiovascular disease

Since the FDA label change, various studies have been published regarding the cardiovascular risks that may be introduced with exogenous provision of T. In 2015, Sharma et al. published a unique investigation in that it included serum T concentrations for all men. In men who continually failed to attain therapeutic concentrations of T with TRT displayed higher rates of myocardial infarction, stroke, and death compared to men who achieved therapeutic serum concentrations. In men with persistently low serum concentrations, the risks of myocardial infarction and stroke were similar to the risks seen in men not given TRT [36]. A follow-up investigation from the same authors included over 50,000 total men and found that the achievement of therapeutic levels of T after TRT conferred a reduced risk of atrial fibrillation compared to untreated men [37]. Similarly, a 2017 investigation also analyzed serum T levels of over 12,000 veterans in a Veterans Administration system and found that therapeutic serum T concentrations with TRT conferred a lower risk of myocardial infarction and death than non-therapeutic treatment T levels [38]. One study of 934,283 subjects from an insurance claims database demonstrated that TRT use did not correspond to higher risks of myocardial infarctions. There was, however, a minimally elevated risk of myocardial infarction after first exposure to TRT [39].

Another 2016 study published soon after revealed that men with longer total TRT exposure displayed reduced rates of adverse cardiovascular events compared to men with short-term use of TRT [40], potentially indicating a protective effect of longer exposure that might alleviate risks seen in early TRT initiation. Shortly after, two more 2017 studies demonstrated a cardioprotective effect of TRT [41, 42]. More recently, a study from 2020 examined TRT in 805 men and reported that TRT of up to twelve years improved various parameters of cardiometabolic health [43]. Finally, a 2021 cohort study of 602 German men with hypogonadism but without baseline cardiovascular disease found that TRT reduced the incidence of new cardiovascular events compared to untreated men, with 45 cases of myocardial infarction or stroke in

the control group and 0 cases in the treatment group after controlling for confounders. This study closely tracked serum T concentrations [44].

Cardiovascular mechanisms of T

Sex hormones are suggested to be partially responsible for the sex-specific differences in cardiovascular disease seen among men and women [45, 46]. The physiological mechanisms behind these differences are illuminated by both in vitro and human reports on cardiovascular function. While some mechanistic explanations may underly adverse effects of T, others could explain potential sources of cardioprotective effects.

Atherosclerosis is a fundamental piece of cardiovascular disease. The administration of T in castrated rabbits fed high-cholesterol diets appears to reverse aortic atherosclerosis [47], while hypogonadal mice fed high-cholesterol diets that are given T demonstrate reversal of lipid accumulation within the aorta [48]. Mice with a knockout *Ar* gene, which encodes for the androgen receptor, exhibit progressively worsening atherosclerosis [49]. In humans, the effect of T on atherosclerosis is less conclusive. The Testosterone Trials, a large group of RCTs, had conflicting results regarding plaque formation. Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM), a trial of 308 men, found und no alterations in carotid intima-media thickness in men treated with TRT. A 2021 investigation of TRT in 157 transgender men displayed increases in leukocyte-endothelium interactions, adhesion molecules, and inflammatory markers with TRT [50].

Lipid profiles also have a direct relationship with cardiovascular disease. However, the effect of T on lipid profiles in humans lacks clarity. T has been shown to diminish total cholesterol, LDL cholesterol, and triglycerides while also diminishing HDL cholesterol [51–53]. Given the positive impact of HDL cholesterol and the detrimental effect of elevated total cholesterol, LDL, and triglycerides, the effect of decreasing levels of all of these molecules simultaneously remains difficult to interpret. In vitro studies corroborate the findings that T enhances hepatic cholesterol absorption and lowers serum cholesterol and LDL [54, 55].

The most commonly cited adverse effect of TRT is erythrocytosis, which has been reported as early as 1992 [56]. Elevated red blood cell levels can diminish blood flow and increase hypercoagulability [57]. Erythrocytosis in TRT may also be influenced by decreased expression of hepcidin, an iron regulatory molecule that may indirectly enhance erythropoiesis via enhanced iron transport [58]. A small study also cites an effect of T on erythrocyte malleability by altering the prevalence of fatty acids in red blood cell membranes, augmenting hemodynamic flow and counteracting the detrimental effects of elevated viscosity [59]. It remains unclear why TRT does not appear to influence the rate of thromboembolic events in men. There have been several studies assessing the use of different testosterone therapies and their effects on erythrocytosis. A study by Pastuszak et al. assessed the use of testosterone gels, testosterone pellets, and testosterone injections in hypogonadal men. They found that the rate of erythrocytosis in men using gels, pellets, and injections was 12.8%, 35.1% and 66.7%, respectively [60].

T has also been shown to influence both cardiac contractility and cardiomyocyte electrophysiology. In rats, orchiectomy-induced hypogonadism demonstrate reduced cardiac contractility that is reversed by T [61]. Additionally, isolated rat ventricular cardiomyocytes display quicker cardiomyocyte relaxation after T exposure [62]. Ventricular myocytes from guinea pigs display shorter repolarization action potentials after T exposure, which relies upon changes in potassium channels and L-type calcium channels [63]. In human studies, hypogonadism is associated with prolonged QT intervals [64], spurring suggestions that diminishing levels of T with aging contribute to the age-related prolongation of QT intervals [65]. One study even found that TRT alleviated the risk of torsades de pointes in hypogonadal men [66]. Further, TRT enhances cardiac output and overall aerobic capacity in men with heart failure [67, 68]. Overall, evidence suggests that T may confer beneficial effects on cardiac physiology.

TRT and randomized controlled trials

Several RCTs published between 1977 and 2012 evaluated the cardiovascular effects of TRT, most commonly by using exercise tolerance and capacity as a proxy for cardiovascular health. Some trials investigated the influence of TRT on ECG alterations during exercise in individuals with chronic stable angina [69–74], while others investigated its influence on exercise in individuals with congestive heart failure [67, 68, 75, 76]. Overall, TRT diminished signs of ischemia on ECG and increased exercise capacity. However, most of these early trials lacked sufficient power, utilizing a maximum of 87 total patients.

More recent RCTs were published after the FDA Advisory Committee meeting. Two trials included TRT but did not evaluate primary outcomes of cardiovascular health, instead examining the impact of TRT on ejaculatory function [77] and pain perception in hypogonadal men [78]. Nevertheless, neither study indicated adverse cardiovascular events in either the treated or placebo group. Other trials utilized primary outcomes related to MetS. A 2016 trial included 44 hypogonadal men who took either placebo or intramuscular T for approximately 6 months and found that insulin sensitivity dramatically increased in men treated with TRT, with the control group displaying no alteration in insulin resistance [79]. A second 2016 trial included 334 men in Japan and demonstrated that one year of TRT resulted in reduced waist circumference, reduced serum triglycerides, and improvements in the short form-36 health survey (SF-36). There was no significant difference in adverse cardiovascular events between the treatment and control group [80].

The most extensive and relevant RCTs are the Testosterone Trials, published in 2016 and 2017, which consist of seven trials from various institutions that sought to investigate the effect of TRT on sexual health, erythropoiesis, bone mass, coronary artery disease, and cognition. In the cardiovascular-related studies of the T Trials, 138 men were monitored for non-calcified and calcified coronary artery plaque volume and coronary artery calcium scores via CT angiography [81]. TRT of one year duration did not increase calcified plaque and did not result in any differences in adverse cardiovascular events between the two groups. However, non-calcified plaque volume increased in the TRT group. Of note, non-calcified plaque volume is not a predictor of adverse cardiovascular events [82], while coronary artery calcium scores are a predictor of such events [81]. The trials did not demonstrate a difference between the two groups in coronary artery calcium scores. The TEAAM trial, which included 308 men, also examined coronary artery calcium scores as well as common carotid artery thickness. The trial did not find any differences between the experimental and control group in artery thickness or in coronary artery calcium scores after three years of treatment with TRT or placebo [83]. No adverse cardiovascular events were reported in either group.

A more recent and broader meta-analysis from 2018 aggregated 31 RCTs and saw no changes in cardiovascular disease with TRT [84], which aligns with two meta-analyses published soon after the FDA Advisory committee meeting [85, 86]. In sum, there is no indication from recent RCTs that TRT increases cardiovascular morbidity or mortality.

Future directions

Although various RCTs attempt to characterize the cardiovascular safety of TRT, most of these trials lack sufficient power or do not evaluate cardiovascular events as a primary outcome. Other factors that could influence the reliability of data include type of T formulation, duration of treatment, inclusion criteria, existing

cardiovascular risk, and lack of serum T level monitoring [87, 88]. Indeed, the T Trials are more directly designed to measure the risks of TRT, yet the longest RCT is a 3-year investigation.

In 2020, several reviews of literature further summarized the current evidence regarding TRT, with all articles commenting that more RCTs are needed to properly evaluate the cardiovascular risks of TRT [89–95]. The TRAVERSE trial commenced in 2018 and is designed to fill this gap in knowledge. The trial is a large RCT that will have greater power and is designed to clarify the relationship between TRT and cardiovascular health [96]. So far, the trial randomly assigned 6000 men with hypogonadism and high risks of cardiovascular disease to receive either topical T or a placebo. The trial is scheduled to maintain a duration of five years, with primary outcomes to include time to adverse cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke or overall cardiovascular mortality. The TRAVERSE trial will provide a clearer answer to the question at hand.

CONCLUSIONS

Testosterone is a key component of cardiovascular physiology. Despite some studies showing an increased rate of adverse cardiovascular outcomes with TRT, most studies do not directly support this finding. Given that most RCTs have so far been unable to establish conclusive evidence, the larger TRAVERSE trial will likely bring crucial findings regarding the safety of TRT. In the meantime, discussion of the benefits of TRT should accompany an honest conversation about its risks, and clinicians should carefully monitor upcoming developments that will paint a more coherent picture of the safety of TRT.

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AUTHOR CONTRIBUTIONS

JA was responsible for conducting the search for eligible studies, screening eligible studies, interpreting results, original draft writing, and draft revision. MK was responsible for conceptualization, screening eligible studies, and draft revision.

COMPETING INTERESTS

MK, MD, MBA, MPH. Consultant: Clarus, Boston Scientific, Metuchen, AbbVie. JA declares no competing interests.

ADDITIONAL INFORMATION

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