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Incidence of Coronary Artery Disease and Testosterone Replacement Therapy

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Abstract

In the United States, males see a decrease in testosterone levels around the age of 40, potentially leading to a condition known as hypogonadism. Testosterone administration is the leading treatment for symptomatic hypogonadism. Testosterone Replacement Therapy (TRT) has increased in popularity amongst practicing healthcare providers. This literature review aims to investigate differences in incidence rates of cardiovascular events in males receiving testosterone therapy compared to untreated males with hypogonadism. Given the conflicting evidence regarding the association between exogenous testosterone and cardiovascular risk, published studies and meta-analysis were reviewed to prove this relationship. A comprehensive literature review was performed using electronic databases such as the American Endocrine Association, Pub-Med, Clinical Key, Cochrane library, and the American Journal of Medicine. A review of the literature shows conflicting data. Various studies showed cardioprotective benefits of TRT, while other studies show an increased incidence of cardiovascular disease. The largest meta-analysis to date revealed no increased cardiovascular risk in men who received testosterone and reduced cardiovascular risk among those with metabolic disease. However, the following studies were limited in duration, dosages, administration routes, and subject population. Because of the inferior quality of evidence, it is challenging to produce a definitive conclusion on cardiovascular disease in males on TRT. Therefore, given the challenge of varied study controls and protocols to assess for rare outcomes, further studies are needed to clarify the association between the duration of TRT and primary adverse cardiovascular effects.

Keywords: testosterone, TRT, Coronary Artery Disease, hypogonadism, eugonadal, hormone replacement therapy

Introduction

Testosterone is the principal sex hormone in males. As males age, testosterone levels decrease. In the United States, the average period of this decrease in testosterone levels begins around age 40. This decrease in natural testosterone production and utilization can generate several health concerns in males. Recent epidemiology studies show that low testosterone levels can be associated with increases in atherosclerosis, coronary artery disease (CAD), and cerebrovascular risks. Testosterone Replacement Therapy (TRT) is becoming a more widely accepted treatment option for males that carries many protective health benefits. With the increasing use of several TRT protocols, including long-term TRT use, a concern for increased cardiovascular and cerebrovascular risk arises. TRT may be a contributing factor to increased incidences of CAD. Investigating studies are in the process are evaluating the contribution of testosterone replacement to the development of CAD. The purpose of my research is to determine if TRT increases the incidence of CAD when compared to untreated hypogonadal males.

Statement of the Problem

Heart disease is the leading cause of death for men in the United States, killing 357,761 men in 2019. That is 1 out of every four male deaths (CDC, 2021). Males continue to surpass females in overall risk factors for CAD. The two most common factors include physical stress and abdominal fat. There is controversy currently on whether a male's testosterone level correlates with the development of cardiovascular disease. Males with insufficient levels of testosterone are diagnosed with hypogonadism. Hypogonadism is a clinical syndrome that results from the failure of the testes to either produce an effective physiological concentration of testosterone or a normal number of spermatozoa. Both domains of hypogonadism affect some

males. Gonadal insufficiency or failure is because of pathology at one or more levels of the hypothalamic-pituitary-testicular axis. Males diagnosed with hypogonadism are often treated with exogenous testosterone replacement therapy. The increased testosterone levels produced by TRT administration are beneficial to patients with symptomatic hypogonadism. They can improve quality of life, as common symptoms include decreased energy levels and sexual dysfunction. Medical providers need to be informed of recent studies and data to treat patients safely and effectively with TRT while mitigating cardiovascular risk. By applying evidence-based medicine to a select patient population, healthcare professionals will feel more confident in the shared decision-making process with the patient who is prescribed TRT. Because of the controversial nature of recent studies showing potential for exacerbated cardiovascular risks and incidence with the administration of exogenous testosterone, there needs to be a consensus on male selection criteria. The Food and Drug Administration has placed restrictions on TRT based on recent studies correlating increased cardiovascular incidence in males treated for hypogonadism. The studies included within this research evaluate the correlation between TRT administration and cardiovascular incidents.

Research Question

In males with hypogonadism, does testosterone replacement therapy (TRT), compared to no hormone replacement therapy (HRT), increase coronary artery disease (CAD)?

Methods

I performed a comprehensive literature review using electronic databases, including PubMed, Access Medicine, the American Academy of Endocrinology (AAE), and the European Association of Urology (EAU). Keywords included testosterone replacement therapy, coronary artery disease, cardiovascular risk, and hypogonadism. The keywords were searched within the

library for peer-reviewed randomized studies, cohort studies, and case-control studies published in English indexed from 2003 to 2020. An independent literature review involved reviewing each study's abstract and full text to determine eligibility. Studies were included if there was a control group that was administered a placebo or no TRT initiation in addition to the TRT intervention group. The reviewer's primary focus was on serious adverse cardiovascular events defined as cardiovascular death, myocardial infarction, acute coronary syndrome, stroke, and mortality. A review of the current literature shows a correlation between testosterone levels and CAD, with a discrepancy between high versus low testosterone levels. Currently, the recommendations for TRT use from the American Academy of Endocrinology (AAE), the European Association of Urology (EAU), and the Food and Drug Administration (FDA) vary.

Literature Review

Theme 1: Effects of testosterone on cardiovascular health in males.

Testosterone has many effects on a male's ability to maintain overall health. TRT includes the exogenous administration of testosterone. Exogenous administration of a hormone means the hormone is given externally versus endogenous hormones that are naturally produced by the body. When increasing or applying an exogenous form of a naturally occurring hormone, there is a concern for potential negative side effects.

Testosterone levels also play a role in the body's cholesterol synthesis, which affects cardiovascular health. There is evidence that varied testosterone levels induce alterations to the lipoprotein profile. Changes to the lipoprotein levels include elevations of low-density lipoprotein (LDL) and decreases in high-density lipoprotein (HDL) (Glazer, 1991). In 2012, researchers Gårevik et al. performed a trial study investigating whether a single dose of testosterone affected cholesterol biosynthesis and HMG COA reductase (HMGCR) expression.

HMGCR is the rate-limiting enzyme of cholesterol biosynthesis. The expression level of this membrane-bound enzyme is controlled by many factors that regulate cholesterol synthesis and cellular cholesterol homeostasis (Edwards, 2003). The study involved 39 male volunteers. They were given a single 500-milligram dose of testosterone enanthate, and researchers analyzed changes to the subjects' cholesterol levels. Their cholesterol levels were measured before and two days post-administration. They used a western blot method on whole blood samples to look for protein expressions of HMGCR. In vitro studies were performed in a human liver cell line to determine whether testosterone regulates mRNA expression of HMGCR. The results concluded that two days post-injection, there was an increase in total cholesterol level by 15% ($p=0.007$). The researchers noted notable changes that included elevations of low-density lipoprotein and decreases of high-density lipoprotein. Elevations of this lipid profile may be associated with an increase in CAD. They concluded that the immediate testosterone administrations alterations on lipids are a cause of concern because of cholesterol alterations, including a rapid rise in LDL. Although, changes in cholesterol levels may naturally develop over life based on various lifestyle factors. This study lacked the data necessary to evaluate TRT's long-term effects on the lipid panel. This was a small-scale study that showed a short duration of effect. This study gives weight to the concern that long-term testosterone administration will affect lipids and increase cardiovascular risk. Increased levels of various lipids may contribute to increased cardiovascular risk.

Testosterone levels play a role in influencing increases in levels of cholesterol. Increased levels of cholesterol have been a contributing factor to atherosclerosis. Plaque deposits on the artery wall, leading to a narrowed passageway for blood to travel. Blood flow may also decrease when there are excess red blood cells. Men over 50 receiving TRT are at a greater risk for

developing erythrocytosis and a hematocrit greater than 52%. When this occurs, a condition known as polycythemia is present. Elevations in hematocrit lead to increased viscosity, a significant risk for venous thrombosis (Bhagi et al., 2019).

In 2018, Ohlander et al. performed a PubMed literature review, considering articles addressing testosterone therapy, erythrocytosis, and polycythemia. The researchers found that men treated with TRT had an increased risk of developing erythrocytosis compared to the control group. They primarily saw this with short-acting injectable formulations. There is a correlation between testosterone replacement therapy and erythrocytosis when looking at the role of hepcidin, iron sequestration and turnover, erythropoietin production, bone marrow stimulation, and genetic factors. At higher blood viscosity, there is an increase in the potential for coronary and cerebrovascular events. Testosterone may increase red blood cell production. There is limited evidence supporting this. They primarily saw the risk in individuals given short-acting esters with supraphysiological testosterone levels. The mechanism of erythrocytosis correlation with thromboembolic events remains unclear. The researchers conclude there needs to be a large multicenter randomized controlled trial looking at testosterone replacement therapy and its effects on hemoglobin and hematocrit.

Besides Ohlander's study, various forms of testosterone application vary. In a study by Maggio et al. in 2012, 108 men over 65 years old with testosterone levels less than 475 ng/dl were randomized to 36 months of testosterone patch vs. placebo in a double-blind fashion. The researchers looked at testosterone's effects on overall erythropoietin (EPO) levels. EPO is a hormone that increases the rate of production of red blood cells in response to low levels of oxygen in the tissues. The study used serum from 67 men, 43 from treatment, and 24 from the placebo group to determine testosterone, hemoglobin, and EPO assays. They did this with

samples from before and after TRT treatment. An important fact was that the serum used was ten years old at the time of the study. There is concern that the age and quality of the sample may be degraded. Mean testosterone and hemoglobin levels increased significantly in the treatment group. Still, they observed no significant changes in EPO between the treatment or placebo groups (Treatment-by-time: $\beta = -0.24$, SE = 2.16, $p = 0.9$). The study found that after 36 months of TRT, there was no increase in erythropoietin. No change occurred in the placebo group either. The study was limited because of the length of serum storage. The samples were stored frozen for ten years. This study proves that further research is needed to ascertain the increase of hemoglobin seen with TRT administration.

Association between TRT and changes in overall blood indices continues to be a concern amongst researchers. In 2010, Fernández-Balsells et al. conducted a systemic review and meta-analysis of various testosterone trials to evaluate the adverse effects of TRT. They developed a systemic review protocol with input from members of the commissioning Task Force from The Endocrine society. They used search bases, such as MEDLINE, EMBASE, and Cochrane, reviewing studies from 2003 to 2008. The studies included comparative, randomized, and non-randomized results that report testosterones effects and outcomes. Subject criteria were adult males with low to low-normal testosterone levels who were treated with any testosterone formulation for a minimum of three months. This identified 51 studies that were reviewed. Considered TRT protocols varied from low to medium doses, with follow-up dates ranging from three months to three years. The researchers abstracted the following descriptive data from each study: description of study participants (age, baseline testosterone levels) and characteristics of treatment and control interventions (testosterone formulation, dose, frequency, route of administration, and treatment duration). To define causes of inconsistency and subgroup-

treatment interactions subgroup participants, subgroups were looked at with the following factors: type of interventions: (testosterone formulation, route of administration, and dose), Outcome characteristic: duration of follow-up (less than six months vs. more than six months). Study quality measure: proportion of patients lost to follow-up (10% or less vs. more than 10%), concealment of allocation, blinding of patients, health care professionals, data collectors, and outcome assessors. The primary aim was to look at death, cardiovascular events, risk factors, and erythrocytosis. The meta-analysis found no significant difference in the parameters of death and cardiovascular events between the testosterone and placebo/nonintervention groups. Testosterone treatment was associated with a significant increase in hemoglobin [weighted mean difference (WMD), 0.80 g/dl; 95% confidence interval (CI), 0.45 to 1.14] and hematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01), and a decrease in high-density lipoprotein cholesterol (WMD, -0.49 mg/dl; 95% CI, -0.85 to -0.13). Increases in hemoglobin, hematocrit, and systolic and diastolic blood pressure were dose-dependent, and intramuscular administration was the route associated with the most dramatic increases. Because of increases in the red blood cell indices with testosterone therapy, this data supports the Endocrine Society Clinical Practice Guideline that providers should monitor hemoglobin and hematocrit in men receiving TRT. This meta-analysis showed a significant correlation between TRT and increased CAD risk factors. The evidence they reviewed produced variable factors. The greatest limitation is the short duration of the TRT trials reviewed. The study data could be incorrect because of baseline testosterone levels. They note that the baseline testosterone level affects the responses of hemoglobin and hematocrit. Subjects that had lower baseline testosterone presented with more increases in both indices. Varied population and health conditions add to this meta-analysis's complexity and variable

nature. It is hard to determine the participants' baseline health of comorbid conditions. This leads to variation in bias for various researchers, focusing on different aspects of TRT.

In conclusion, the cited studies had many strengths and weaknesses. The data from all these studies showed limitations and variations in data collection. These researchers focused on testosterone's ability to alter RBC indices and lipid profiles in correlation to overall cardiovascular health. They failed to determine the long-term effects of TRT administration, for the studies were limited in duration of time. A common weakness shared amongst the studies was the initial screening criteria. They extrapolated data from older male populations. There need to be further studies with standardized dosages and diverse subject populations.

Theme 2: Cardiovascular incidence on TRT

In 2016, researchers Albert and Morely performed an electronic literature search for human studies regardless of language between 2013 and February 2017 using a search strategy of 'testosterone,' 'random' and 'trial.' They defined a cardiovascular event as death, myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, coronary bypass, syncope, arrhythmia, admission to the hospital for congestive heart failure, or cerebrovascular event. Forty-five randomized controlled trials, including three meta-analyses, were reviewed. The researchers excluded studies looking at supraphysiological testosterone dosages and studies of <40 years. There were 45 trials with 5328 subjects evaluated, with a mean age at initiation of therapy of 63.3 (SD ± 7.9) years, with a mean study duration of 10.6 (± 8.6) months. The mean enrolment testosterone level was 11.1 (± 3.3) nmol/l. Many studies used a serum testosterone level of <12 nmol/l as an enrollment threshold for testosterone deficiency. The mean therapeutic testosterone levels were 20.5 (± 6.9) nmol/l. Twenty studies used transdermal testosterone as the mode of transportation (n=3366 subjects), 19 studies used intramuscular testosterone (n=1228

subjects), and only five studies used oral testosterone (n=734). Overall, there was no increase in cardiovascular risk for the entire cohort, risk ratio (RR) = 1.10 (95% CI 0.86: 1.41, P = 0.45). A funnel plot showed no apparent publication bias. For the entire cohort, there was no difference in the risk ratio for age less than or greater than 65 years, mode of testosterone supplementation, initial testosterone level less than or greater than 12 nmol/l, or therapeutic testosterone levels in clinical cardiovascular outcomes. The researchers performed a subgroup analysis that showed an increased rate of cardiovascular events in studies with fewer than 12 months compared to longer duration studies. There was an excess cardiovascular event rate predominantly during the first 12 months after testosterone therapy (n = 2523), RR = 1.79 (95% CI 1.13:2.82, P = 0.012, I2 = 0%). This early increase in cardiovascular event rate was significantly different (p for interaction 0.0004) from those studies over 12 months duration (n = 2569) (RR = 0.87 (95% CI 0.64:1.17, P = 0.356). Within the subset analysis of early cardiovascular events, <12 months, they predominantly found the increased cardiovascular event rate in those ≥ 65 years of age. The risk ratio for cardiovascular events was 2.90 (95% CI, 1.35: 6.21, P = 0.006, I2 = 0%) in those 65 years of age or older. There was no difference in cardiovascular events for different modes of administration. Intramuscular testosterone had a neutral effect on cardiovascular event rates (RR = 0.96 (95% CI 0.46: 1.98. P = 0.91)) compared with the effect of oral testosterone (RR = 2.28, 95% CI 0.60; 8.59, P = 0.22) and transdermal testosterone, (RR = 2.80 (95% CI 1.38; 5.68, P = 0.004)). This analysis suggests we may associate TRT with increased cardiovascular events during the first year of treatment in patients over the age of 65. There is variability in reporting cardiovascular events within the provided studies. Some did not have preset criteria for determining the classification of a cardiovascular event. Several studies noted cardiovascular events as side effects of TRT that became secondary findings. This is difficult to assimilate the

information, as the initial intent of the studies was not to look specifically at TRT and cardiovascular events. Patient demographics were variable. The researchers excluded any study with the patients' age less than 40, limiting the determination of whether TRT increases risk in a younger male population. The data selected from this analysis correlated cardiovascular health and age regardless of route of administration and dosage. A consistent theme between studies is reporting of predisposing risk factors.

Overall, cardiovascular health varies from patient to patient and is based on multiple variables. Cardiovascular-related problems are often secondary to other health concerns. Corona et al. (2017) performed a meta-analysis and systemic review of placebo-controlled randomized clinical trials regarding the effects of testosterone and cardiovascular-related problems. The analysis looked at the effect of TRT, compared with placebo, on the incidence of a new major adverse cardiovascular event. They defined events as cardiovascular death, non-fatal acute myocardial infarction, stroke, and acute coronary syndromes. Heterogeneity in these events was accessed by using I^2 statistics. The authors reviewed 2747 articles and analyzed only 75 articles. Within the 75 articles, the meta-analysis included 3016 TRT patients and 2448 placebo grouped patients. The mean duration of the study was 34 weeks. The authors found that 71 of the 75 articles reported cardiovascular events, acute myocardial infarction, and 74 reports of cardiovascular mortality. There were no significant correlations between TRT and cardiovascular risk through their review. Of the 73 trials reporting cardiovascular events, 47 detected no events; therefore, the main analysis was performed on 26 trials ($p = 0.78$). Funnel plot and Beg adjusted rank correlation test (Kendall's t: -0.14; $p = 0.33$) suggested no major publication bias. Using testosterone was not associated with any significant difference in the incidence of cardiovascular events for the placebo group (MH-OR: 1.01 [0.57; 1.77]; $p = 0.98$) (Figure 2). Meta-regression

analysis showed no difference in the incidence of cardiovascular events according to baseline age, body mass index or level of testosterone (S = 0.03 [-0.04;0.10]; p = 0.40, -0.07 [-0,29;0.14]; 0.51; -0.14 [-1.17;0.89]; p = 0.79]. They performed a sensitivity analysis with continuity correction, confirming the main analysis results (MH-OR: 0.98 [0.70; 1.34]; p = 0.92). This data provides insight into TRT and cardiovascular incidence. Age and duration of treatment limited the study. The average male receiving testosterone was 59 years of age. Variations in age and unreported health history lead to biases in data. The meta-analysis used articles that found cardiovascular events as secondary findings. There are variations in how other researchers selected diagnostic criteria and screening methods for incidents of cardiovascular disease.

As noted by Corona et al., they found the cardiovascular events as secondary findings. Ischemic heart disease is the number one leading cause of death globally. Finkle et al. (2012) conducted a cohort study looking at the risk of non-fatal myocardial infarction following an initial testosterone prescription to 55,594 subjects in a large-health care database. It based this patient population on the hypothesis that testosterone treatments might increase the risk of acute non-fatal myocardial infarction, particularly those with pre-existing cardiac disease. They collected data from the Truven Health MarketScan Commercial Claims and the Encounters Databases, including employees, dependents, and retirees with commercial or Medicare insurance whose employers license health care data to Truven. Within this patient population, they formed cohorts of men with a minimum of 22 months of continuous enrollment. These men had post-prescription follow-up intervals of 90 days. This cohort's subjects were selected based on testosterone prescriptions, not containing estrogen, compared to men who filled a prescription for phosphodiesterase type 5 inhibitors (PDE5I). They chose males prescribed PDE5I as the

comparison group because some indications for PDE5I use are similar to indications for a testosterone prescription.

The research used ICD-9 codes associated with myocardial infarction, including angina, arrhythmia, heart disease, prior MI, heart failure, hypertension, hyperlipidemia, stroke, peripheral vascular disease, and cerebrovascular disease. They compared the rate of myocardial infarction incidence in the 90 days following initial prescription to the year preceding the prescription of TRT. The researchers also compared post/pre rates in a cohort of 167,279 men prescribed phosphodiesterase type 5 inhibitors (PDE5I; sildenafil or tadalafil) and compared testosterone prescription post/pre rates with the PDE5I post/pre rates. In all subjects, the post/pre-prescription rate ratio (RR) for testosterone prescription was 1.36 (1.03, 1.81). In men aged 65 years and older, the RR was 2.19 (1.27, 3.77) for testosterone prescription and 1.15 (0.83, 1.59) for PDE5I, and the ratio of the rate ratios (RRR) for TT prescription relative to PDE5I was 1.90 (1.04, 3.49). The RR for testosterone prescription increased with age from 0.95 (0.54, 1.67) for men under age 55 years to 3.43 (1.54, 7.56) for those aged greater than 75 years ($p_{trend} = 0.03$), while no trend was seen for PDE5I ($p_{trend} = 0.18$). In men under age 65 years, the excess risk was confined to those with a prior history of heart disease, with RRs of 2.90 (1.49, 5.62) for TT prescription and 1.40 (0.91, 2.14) for PDE5I, and a RRR of 2.07 (1.05, 4.11). These results correlate with an increased cardiovascular risk with TRT for males who have a pre-existing diagnosis of heart disease. Previous studies have been vague on the initial diagnosis of hypogonadism and additional diagnoses. The study showed risk stratifications associated with various age groups and different routes and dosages of testosterone. The study looked primarily at the effects of testosterone on cardiovascular health but lacked sufficient information on the diagnostics indications for TRT. The data may not include individuals who are at high risk for

TRT. All forms of testosterone and dosages within this review lack correlations between the dose and route used to assess if this contributes to increased risk. The researchers could get a large amount of data based on the Medicare database used, but it can bias this as it does not include individuals with other insurance forms or self-paid.

In contrast to Finkle's study, mobility can play a role in cardiovascular health. Basaria et al. (2010) performed a research study looking at males aged 65 or older with limited mobility. The study was a placebo-controlled, randomized trial that determined the effects of testosterone administration on lower-extremity strength and physical function in older men with limitations in mobility and low serum levels of total or free testosterone. They selected these subjects with a serum testosterone level of 100 to 359 ng per deciliter (3.5 to 12.2 nmol per liter) or a free serum level of less than 50 pg per milliliter (173 pmol per liter). They required the participants to have evidence of limited mobility. They defined this as having difficulty walking two blocks on a level surface, climbing ten steps, and having a score between 4 and 9 on the Short Physical Performance Battery. Participants were excluded if they had uncontrolled hypertension, unstable angina, and myocardial infarctions three months before enrollment. They randomly assigned these individuals to receive a placebo gel or 100 mg dose of testosterone gel. This gel was to be applied daily for six months. After two weeks, the dose was adjusted if the average of two testosterone measurements was less than 500 ng per deciliter (17.4 nmol per liter), in which case the dose was increased to 150 mg daily, or over 1000 ng per deciliter (34.7 nmol per liter), in which case the dose was decreased to 5 mg daily. A baseline in maximal voluntary muscle strength subjects performed a leg-press exercise to assess efficacy. They extracted secondary efficacy outcomes from changes in baseline chest-press strength, 50-m walking speed, stair-climbing speed and power, and lift-and-lower test. They assessed testosterone levels at baseline

and week 24. They implemented safety monitoring, which included monitoring hemoglobin, hematocrit, prostate-specific antigen, and any adverse events. The researchers looked for any adverse effects of the testosterone treatment in men with mobility limitations. It is of significant value that both study groups had a high prevalence of hypertension, obesity, diabetes, hyperlipidemia, and known cardiovascular disease. They ended their study early because of a significant rate of adverse cardiovascular events in the group receiving the testosterone gel. The testosterone group, when compared to the placebo group, had a significant increase in hemoglobin, hematocrit, and low-density lipoprotein cholesterol levels with a decrease in high-density lipoprotein cholesterol. Neither group exhibited variance in blood pressure readings. There were 209 men with an average of 74 years of age enrolled in this trial. At the beginning of the study, there was a high prevalence of hypertension, diabetes, hyperlipidemia, and obesity among the study group. Throughout the 6-month treatment period, 23 subjects from the testosterone group had a cardiovascular-related adverse event. They compared this to only five subjects within the placebo group. Compared with all other subjects, men with high testosterone levels had a higher risk for cardiovascular-related events (HR 2.4; $p = 0.05$). It is also of significant value that the study failed to mention if there were several individuals with contributing factors to CAD at baseline. The study does not inform the reader whether the individuals who had a cardiovascular event had existing elements known to cause CAD. The study was substantial in sample size, variances in dosing protocols, and direct monitoring of serum levels to show if high testosterone levels increased risk. The trial was limited and ended early because of adverse cardiovascular events. The data is hard to compare when looking at other doses and formulations of testosterone or other population groups.

Contrasting Basaria et al., Calof et al. (2005) performed a study on 651 men who received TRT and 433 men who received a placebo. The inclusion criteria for both groups included men over 45 years old with low to low-normal testosterone levels who were currently receiving TRT for at least 90 days. The researchers did not find any difference in the cardiovascular event between both groups throughout the study. The placebo group had two deaths with an unknown cause. They defined cardiovascular events as the development of arrhythmia, myocardial infarction, chest pain, or ischemia. Eighteen cardiovascular events (2.8%) were observed in the testosterone group compared to the 16 cardiovascular events in the placebo group (3.7%). The combined endpoints were similar between the two groups, with an odds ratio of 1.14% (95% CI, 0.59-2.20). During the study, variables included the form of testosterone (gel, patch, oral, injectable), age range, initial testosterone levels, and study duration. Major cardiovascular endpoints included events such as myocardial infarction, coronary procedure, and death. This study shows no differences in the incidence of cardiovascular events between a patient receiving testosterone and a placebo patient. The study lacks prior data on prior cardiovascular risk factors or any exclusion factors in the subjects. There was a variety of dosages used and variances in the duration of use. One cannot extrapolate data to compare if the dose used or health status was a contributing factor.

Testosterone levels vary from individual to individual and harbor different effects on the overall health picture. Haddad et al. (2007) performed a meta-analysis of 30 randomized, placebo-controlled trials. Eight hundred eight men received TRT, and 834 men received a placebo. They subdivided TRT subjects into low, low-normal, and normal baseline testosterone levels. Comparison of blood pressure between both groups showed no significant changes in systolic or diastolic. Total cholesterol levels were reduced within the TRT group with the most

significant variation within the low-normal and normal baseline testosterone groups (OR: - 0.47; 95% CI, -0.77 to -0.17), whereas LDL and high-density lipoprotein cholesterol (HDL-C) were decreased, and triglycerides were increased without statistical significance. Cardiovascular events were reported in six studies. In those six studies, 161 men receiving testosterone and 147 men in the placebo group had a cardiovascular event. Cardiovascular events included myocardial infarctions, angina or claudication, revascularization, and stroke. Fourteen events (8.7%), including five MIs and one cardiovascular death in the TRT group, and seven events (4.8%), including two MIs and one death in the placebo group, were observed. The pooled OR for cardiovascular events was 1.82 (95% CI, 0.78–4.23), which was not statistically significant. This parameter was only a small fraction out of the 30 randomized trials. The patient populations were not specific or other demographics. Henceforth, based on limited data, one cannot extrapolate contributing factors to cardiovascular events.

Vigen et al. (2013) performed a retrospective cohort study to evaluate the association between TRT and all-cause mortality, MI, or stroke. There were 8709 male veterans with a total testosterone level of <300 ng/dL that underwent coronary angiography. They subdivided the participants into two groups; males who were prescribed TRT, and those who were not. The primary endpoint for this study was a composite of time to hospitalization for MI or stroke. One thousand two hundred twenty-three patients filled a prescription for TRT following their coronary angiography. It was under the assumption that the males would continue to take testosterone up to the point of a cardiovascular event. The male receiving TRT showed a significant increase in cardiovascular incidence compared to no TRT (HR, 1.29 [95% CI, 1.04–1.58]). This value did not assess the continuation of use. Of the 1710 outcome events, 748 men died, 443 had MIs, and 519 had strokes. Among 7486 patients not receiving testosterone therapy,

681 died, 420 had MIs, and 486 had strokes. The Kaplan-Meier estimated cumulative percentages with events among the no testosterone therapy group vs. the testosterone therapy group at one year after coronary angiography was 10.1% vs. 11.3%; at two years, 15.4% vs. 18.5%; and at three years, 19.9% vs. 25.7%. The absolute risk differences were 1.3% (95% CI, −7.1% to 9.7%) at one year, 3.1% (95% CI, −4.9% to 11.0%) at two years, and 5.8% (95% CI, −1.4% to 13.1%) at three years (Vigen et al. 2013).

Among 1223 patients on TRT, 67 died, 23 had MIs, and 33 had strokes. They monitored these patients at 180, 365, and 54- days for follow-up. They associated TRT with increased risk of adverse outcomes, including all-cause mortality, MI, and ischemic stroke (hazard ratio [HR], 1.29; 95% CI, 1.05-1.58; P =.02). They adjusted the data for CAD, and the findings remained unchanged (HR, 1.29; 95% CI, 1.04-1.58). There was no significant difference in the effect size of TRT between those with and without CAD (test of interaction, P =.41).

Baillargeon et al. (2014) performed a retrospective cohort study of Medicare beneficiaries greater than 66 years. There were 6355 patients with hypogonadism treated with TRT and 19,065 untreated individuals. They based an individual treated for TRT on receiving at least one injection of testosterone. They matched a control group at a 1:3 ratio based on the prognostic index score for MI risk. They performed a Cox regression analysis, adjusting for demographic and clinical characteristics. This study showed that TRT was not associated with a higher risk of myocardial infarction when compared to no TRT (RR, 0.84 [95% CI, 0.69–1.02]). For men with the highest score of the MI prognostic score, TRT was associated with a reduced risk of MI (HR = 0.69; 95% CI = 0.53-0.92), whereas there was no difference in risk for the first (HR = 1.20; 95% CI = 0.88-1.67), second (HR = 0.94; 95% CI = 0.69-1.30), and third quartiles (HR = 0.78;

95% CI = 0.59-1.01). Testosterone produced a protective benefit for males with a high risk for myocardial infarction.

Theme 3: Untreated hypogonadism and cardiovascular risk

In the above studies, hypogonadism was another contributing factor to cardiovascular incidences. Corona et al. (2011) performed a meta-analysis to verify whether hypogonadism is a contributing risk factor for cardiovascular event incidence. The authors also wanted to confirm whether TRT improved cardiovascular health in patients with known CAD. They reviewed 1178 articles. Of the 1178 retrieved articles, the researchers included only 70 for their study. Cross-sectional studies showed cardiovascular disease in patient populations that have significantly lower testosterone and higher 17-b estradiol (E2) levels. They confirmed the association between low testosterone and high E2 levels with CVD in a logistic regression model, after adjusting for age and body mass index (hazard ratio (HR) Z0.763 (0.744–0.783) and HRZ1.015 (1.014–1.017), respectively, for each increment of total testosterone and E2 levels; both P>0.0001). Longitudinal studies showed that baseline testosterone level was significantly lower among patients with incident overall- and CV-related mortality than controls. Conversely, the researchers did not observe any difference in the baseline testosterone and E2 levels between case and controls for incident CVD. Finally, TRT was positively associated with a significant increase in treadmill test duration and time to 1 mm ST-segment depression. Through their meta-analysis, the researchers found data that supports testosterone's ability to enhance myocardial function through direct and indirect effects on myocardiocytes.

In theory, hypogonadism leads to an increase in damage to the function of these myocardiocytes following the onset of CAD. The meta-analysis shows that the patients with CAD on average had lower testosterone levels when compared to healthy controls. The

researchers associated higher E2 levels with the prevalence of CAD. This study could pose bias to some factors towards CAD. The researchers limited their results to the effect of TRT on CAD derived from treadmill tests in men with chronic stable angina. This limited their data to a select group of patients.

A retrospective analysis of 1031 men (average age 62 years) with testosterone levels of 250 ng/dL or less from seven Veterans Affairs medical centers found that 398 men who were treated with testosterone replacement therapy had lower mortality than those who were untreated (10.3% vs. 20.7%, adjusted HR 0.61, 95% CI 0.42–0.88) (Shores et al., 2012). Throughout this study, the researchers looked at the duration of treatment on TRT. Other studies have limited their study duration from initial prescription to the event. A follow-up study looked at men 90 days after cessation of TRT. This follow-up study found that TRT was associated with a decrease in mortality. There is a correlation between higher mortality and lower baseline testosterone and shorter duration and treatment.

Low testosterone levels have been associated with an increase in low-density lipoprotein (LDL) and triglyceride levels, two contributing factors in CAD (Kelly, 2013). Grosman et al. (2014), performed a research study evaluating the relationship between testosterone levels and metabolic syndrome in males older than 45. Metabolic syndrome is a cluster of conditions that occur together, increasing your risk of heart disease, stroke, and type 2 diabetes. These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. The study looked at 660 men aged 45 to 70 years old. They derived the initial screening criteria from individuals screened for prostate cancer. The NCEP-ATP III criteria were used to diagnose metabolic syndrome. The researchers found metabolic syndrome was inversely associated with testosterone levels independently of age ($\chi 2$,

$p < 0.001$) (OR 0.802, CI 95%: 0.724–0.887, $p < 0.0001$). This was found by dividing the patient population into four groups based on their testosterone levels (low, low, mid-normal testosterone, and high-normal testosterone). The most common abnormality observed was hypertension, elevated triglycerides, and waist circumference. They noted that low testosterone correlated positively with an increase in HDL (r: 0.14, $p < 0.0001$) and negatively with body mass index.

In aging males, the natural total testosterone levels will decline with age. Grosman's study found that the prevalence of metabolic syndrome increases in men older than 45 years of age with declining testosterone levels. Understanding that metabolic syndrome includes several pathological conditions, we associate all with an increased risk of developing cardiovascular disease and type 2 diabetes. They limited this study in the duration of time. It is of significant value that the study found a higher incidence of metabolic syndrome in subjects with lower testosterone levels. This was seen in 40% of their subject population. The study had a very selective population, as they performed the study on males that had completed a prostatic evaluation to screen for early detection of prostate cancer.

We can assess overall cardiovascular health with various diagnostic tests. Dobrzycki et al. (2003) conducted a clinical study investigating the association of male sex hormones with the extensiveness of coronary heart disease risk factors and ejection fraction of the heart. They performed a coronary angiogram on 96 Caucasian males, resulting in 76 with a positive test and 20 with a negative test. Total testosterone, free testosterone, free androgen index, sex hormone-binding globulin (SHBG), estradiol, luteinizing hormone, follicle-stimulating hormone, plasma lipids, fibrinogen, and glucose levels were collected before the examination. An X-ray was performed using Quantitative Coronary Angiography and Left Ventricular Analysis packages on the TCS Acquisition workstation to assess ejection fraction. Lower testosterone levels (free and

total), free androgen index, and estradiol were found in males with proven coronary heart disease. There was a negative correlation observed in SHBG and lipid profiles in males with low levels of testosterone when compared to healthy controls. It also found that males with low testosterone levels had a lower ejection fraction. This study was the first to capture the correlation between low free-testosterone levels and low ejection fraction. The data is biased for a small population of males of Caucasian descent.

Discussion

Incidence of cardiovascular disease and TRT is clinically relevant because of an increasing number of patients being treated for hypogonadism. The results show a strong correlation between testosterone replacement therapy, cardiovascular risk, and increased cardiovascular incidents. There is also contradicting data comparing individuals with TRT to untreated males. Males treated with TRT show increases in red blood cell indices. The study performed by Ohlander et al. (2018) suggests testosterone plays a role in hepcidin and erythropoietin production, leading to an increase in red blood cell production. Maggie et al. could reproduce this in a randomized study that increased hemoglobin with no noticeable increase in erythropoietin in males receiving TRT. Based on the above studies, the mechanism by which testosterone changes red blood cells indices is unknown. Although, both studies' results included TRT patients with higher hemoglobin and hematocrit levels than the placebo groups.

Variations in lipoprotein levels are presented in studies independent of testosterone levels. Garevik et al. (2012) demonstrated testosterone to increase total cholesterol levels by 15%. Haddad et al. (2007) showed that total cholesterol levels were reduced within their TRT group. The reduction was seen in LDL and HDL; however, triglycerides increased without statistical significance. Kelly et al. (2013) and Grosman et el. (2014) correlate low testosterone levels with

increased LDL and triglycerides. The studies conflict with each other, determining whether TRT or low testosterone levels are contributing factors to changes in lipid profiles. The changes were viewed in both groups.

However, the above physiological changes may contribute to cardiovascular events. A consensus for a cardiovascular event is defined as death, myocardial infarction, acute coronary syndrome, syncope, arrhythmia, and admission to the hospital for congestive heart failure or cerebrovascular events. It is noted in Albert et al. (2016) meta-analysis that cardiovascular events were predominantly seen in the first 12 months after initiation of testosterone therapy. Increases in cardiovascular events were noticed at a higher rate in those greater than 65 years old. Using testosterone was not associated with any significant difference in the incidence of a cardiovascular event compared to the placebo group (Corona et al., 2017). Studies performed by Calof et al., Vigen et al., Haddad et al. showed no correlation between TRT and cardiovascular health.

In contrast to these studies, hypogonadism is a risk factor for cardiovascular events. Corono et al. (2011) performed a meta-analysis to verify whether hypogonadism contributes to cardiovascular events. They observed that baseline testosterone levels were significantly lower among patients with incident overall and CV-related mortality, in comparison with controls. In theory, hypogonadism increases damage to the function of myocardiocyes following the onset of CAD. Dobrzycki et al. (2003) could show this correlation with assessing ejection fraction. Patients with lower ejection fractions had lower levels of testosterone when compared to controls.

I found the studies in this review to be limited to various factors. The most common factors include the duration of the research and the age of subjects. There was no data provided

for young, healthy males who are being treated primarily for hypogonadism in the studies. This limitation hinders the ability to extrapolate data to all patient populations. Each study had different inclusion and exclusion criteria, but most did not mention screening for existing cardiovascular risk factors—this literature review ties into concepts that support an increase in the incidence of CAD and TRT administration. More information is to be researched to include various hormone levels in cardiovascular health.

Applicability to Clinic Practice

This study aimed to determine if TRT increases the incidence of CAD when compared to untreated hypogonadal males. Incidence of cardiovascular events was observed in both groups. It was observed that testosterone increased these two variables. However, testosterone's ability to alter red blood cell indices and lipid profiles may hinder the application of TRT. Based on the data provided in this literature review, providers must ensure all risk factors for cardiovascular health are documented and addressed before initiation of TRT. Prescribing TRT should be used with caution, and providers should adequately monitor patients. Patients' blood pressure, hemoglobin, hematocrit, and cholesterol should routinely be assessed at regular intervals and monitored for any adverse effects. Providers must use discretion and clinical reasoning to incorporate the patient's health history into treatment protocols for TRT. Understanding that elderly males over the age of 65 demonstrated cardiovascular events, we should use discretion to avoid complications in this patient population.

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