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INVITED REVIEW

Male Endocrinoogy

Controversies in testosterone replacement therapy: testosterone and cardiovascular disease

Kathleen Hwang[1], Martin Miner[2]

The role of testosterone in the cardiovascular (CV) health of men is controversial. Data suggest that both the condition and treatment of clinical hypogonadism is associated with decreased CV mortality; however, two recent studies suggest that hypogonadal subjects treated with testosterone replacement therapy have a higher incidence of new CV events. There has been increased media attention concerning the risk of CV disease in men treated with testosterone. Until date, there are no long-term prospective studies to determine safety. Literature spanning over the past 30 years has suggested that not only is there a possible increased CV risk in men with low levels of testosterone, but the benefits from testosterone therapy may even lower this risk. We review here the recent studies that have garnered such intense scrutiny. This article is intended as a thorough review of testosterone levels and CV risk, providing the clinician with the facts needed to make informed clinical decisions in managing patients with clinical hypogonadism.
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INTRODUCTION

Testosterone replacement therapy (TRT) is a well-established method of managing men with testosterone deficiency, commonly referred to as male hypogonadism, since it was first introduced in the mid-1930s. Concerns over reports that castration or estrogen treatment designed to lower testosterone to castrate levels, caused amelioration of metastatic prostate cancer, and that TRT potentially activated prostate cancer led to a significant decrease in the utilization of TRT to treat testosterone deficiency until new formulations developed in the early 2000s and improved ease and convenience of treatment. Treatment prior to this period was reserved for the most severe cases of testosterone deficiency such as in young men with pituitary etiologies of primary testicular failure or testicular cancer survivors. However, over the past decade there has been an exponential increase in the use of TRT. Recent reports have noted a more than 3-fold increase in testosterone prescriptions over the past decade. This is a result of increased physician and patient awareness of hypogonadism as a disease process as well as the benefits of treatment complemented by the increased convenience of testosterone formulations.

Hypgonadism is defined as a clinical syndrome, which comprises both symptoms and biochemical evidence of testosterone deficiency.[1,2] Clinical guidelines have provided some direction for normal levels for testosterone, but differences in the measurement of testosterone between assays and laboratories often lead to problems interpreting these thresholds.[3] The diagnosis of hypogonadism remains controversial, however, there has been a growing body of literature regarding the negative impact of low testosterone on male health making it a growing concern for many clinicians. There continue to be numerous controversies associated with TRT, including cardiovascular disease (CVD).

Recently, two studies reporting an increased CV risk in men who received TRT have received significant media attention. Although a substantial volume of literature over the past 30 years has suggested that low testosterone concentrations are associated with CV risk and that TRT has been show to offer significant therapeutic benefits, the media has utilized these recent reports to promote the idea that TRT is dangerous. These recent events have created a difficult situation for clinicians and their patients.

Unfortunately, the recent reports linking TRT to CVD fail to provide an objective and complete assessment and fail to show that TRT increases CV risk. In the following paper, we examine the studies that have gained recent attention regarding TRT and increased CV risk, in addition to providing a broad review of the literature regarding TRT in the setting of hypogonadism and decreased CV risk.

TESTOSTERONE AND MORTALITY STUDIES

There is supporting evidence from both clinical studies and those investigating surrogate markers that there is a link between low testosterone and CVD.[4,5] Furthermore, longitudinal epidemiological studies and other clinical studies showed increased CV mortality in men with testosterone deficiency.[6–8] Of the studies reported evaluating mortality, the major cause of increased mortality was mostly attributable to CVD (**Table 1**).[7,9–22]

In the Rancho-Bernardo study, 264/529 deaths were attributable to CVD, which persisted after excluding deaths up to 5 years.[9] Low total testosterone (TT) was associated with central obesity, insulin resistance, hyperglycemia, blood pressure, and dyslipidemia as well as emerging risk factors such as leptin and C-reactive protein (CRP). In the European Prospective Investigation into Cancer in Norfolk-Norfolk

[1]Department of Surgery (Urology), The Alpert Medical School of Brown University, Providence, Rhode Island, USA; [2]Department of Family Medicine, The Alpert Medical School of Brown University, Providence, Rhode Island, USA.
Correspondence: Dr. Kathleen Hwang (kathleen_hwang@brown.edu)
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Table 1: Impact of baseline testosterone levels on CVD mortality

Author, year (study name)	*Country*	*Population studied*	*n*	*Follow-up*	*CVD mortality HR/OR for TT unless indicated (95% CI)*
Smith *et al.*[22]	UK	Population based	2512	16.5 years	HR: 0.94 (0.80-1.11) (NS) IHD
Khaw *et al.* (EPIC-Norfolk)[11]	UK	Population based	2314	7 years	OR quintile 2, 3, 4 versus 1 CVD 0.89 (0.60–1.32) 0.60 (0.39–0.92) 0.52 (0.32–0.86) CHD 0.71 (0.43–1.17) 0.59 (0.39–1.00) 0.52 (0.28–0.97)
Araujo *et al.* (MMAS)[12]	USA	Population based	1686	15.3 years	RR FT: 0.80 (0.64–0.99), *P*=0.02 for trend
Laughlin *et al.* (Rancho-Bernardo study)[9]	USA	Population based	794	11.8 years	HR: 1.38 (1.02–1.85)
Carrero *et al.*[17]	Sweden	Hemodialysis	126	41 months	HR: 3.19 (1.49–6.83)
Vikan *et al.* (Tromso)[13]	Norway	Population based	1568	11.2 years	HR: FT: 1.24 (1.01–1.54)
Haring *et al.* (SHIP)[7]	Germany	Population based	1954	7.2 years	HR: 2.56 (1.15–6.52)
Menke *et al.* (NHANES)[18]	USA	Population based	1114	18 years	HR: baseline-year 9 FT: 1.53 (1.05, 2.23) TT: NS Year 9–18: NS
Corona *et al.*[10]	Italy	Erectile dysfunction	1687	4.3 years	HR: 7.1 (1.8–28.6)
Malkin *et al.*[19]	UK	CHD (-angiogram)	930	6-9 years	HR BT: 2.2 (1.2–3.9) T: 2.5 (1.2–5.3)
Haring *et al.*[20]	Germany	CKD, albuminuria, kidney dysfunction	1822	9.9 years	HR: 2.01 (1.21–3.34)
Kyriazis *et al.*[14]	Greece	Hemodialysis	111	37 months (median)	HR: 2.92 (1.08–7.87)
Lerchbaum *et al.*[15]	Austria	Coronary angiography referrals	2069	7.7 years	HR: 1.77 (1.23–2.55)
Hyde *et al.* (Health in men study)[16]	Australia	Population based	4249	5.1 years	HR: 1.71 (1.12–2.62)
Haring *et al.* (Framingham heart study)[21]	USA	Population based	254	5 and 10 years	HR: 0.74 (0.56–0.98)

TT: total testosterone; BT: bioavailable testosterone; FT: free testosterone; HR: hazard ratio; OR: odds ratio; NS: not significant; EPIC-Norfolk: European Prospective Investigation into Cancer in Norfolk; MMAS: Massachusetts Male Aging Study; NHANES: Third National Health and Nutrition Examination Survey; SHIP: Study of Health in Pomerania; CHD: coronary heart disease; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; CI: confidence interval; IHD: ischemic heart disease; RR: relative risk

study, the quartile of men with the lowest testosterone levels had the shortest survival, and the quartile with the highest testosterone levels showed the longest survival;[11] 369/825 deaths were due to CVD, which persisted after age and covariate adjustment. It is also of interest that a subgroup of men who received treatment to normalize their decrease in their testosterone levels had the same survival as those of men who had a normal testosterone level. This study concluded that endogenous testosterone levels are inversely related to body mass index (BMI), waist-hip ratio and prevalence of type 2 diabetes.

DECREASED TESTOSTERONE AND MARKERS OF CARDIOVASCULAR MORTALITY

Clinicians and investigators have identified clinical and biochemical markers that are shown to be increased risk factors for CVD. These include increased BMI, altered serum lipid levels and coagulation profiles, high blood pressure, insulin resistance, and increased inflammation.[23] One example is CRP, an inflammatory marker, where one study looking at the relationship between testosterone concentrations and high sensitivity CRP noted that lower levels of serum testosterone were associated with the highest levels of CRP.[24]

The severity of coronary heart disease (CHD) as evaluated by >75% stenosis of one, two, and three vessels was associated with significantly higher serum interleukin-1β and lower interleukin-10 and lower testosterone levels.[25] Decreased testosterone levels are related to increased atherosclerosis, especially of the carotid arteries. Carotid intima media thickness (CIMT), a surrogate marker for the degree of *in vivo* atherosclerosis is commonly used as a subclinical marker and a common outcome measure in most studies on disease progression and effects of treatment including testosterone supplementation. One study demonstrated that after a 4-year follow-up period, men who were in the lower tertile of testosterone had the greatest increase of CIMT.[26] Low testosterone levels were related to CIMT independent of other CV risk factors, and a reduction of CIMT is demonstrated in response to TRT.[26,27]

Testosterone levels in the acute setting may also predict clinical outcomes after a coronary event. In 126 consecutive male patients admitted with acute myocardial infarction (MI), a recent study demonstrated that low testosterone levels on admission were independently related to higher mortality after 30 days.[28] A prospective cohort study evaluated a consecutive series of 1687 men seen at an Andrology Clinic and found that low testosterone levels were associated with a higher mortality from major adverse CV events.[10]

Testosterone and mortality in diabetes

Low testosterone is associated with insulin resistance, metabolic syndrome, and type II diabetes mellitus (DM).[29] This direct effect on insulin sensitivity has been demonstrated experimentally and thought to be mediated via mitochondrial function.[30] A recent study evaluated the effect of baseline testosterone on mortality in men with type II DM over a mean follow-up period of 5.8 years.[31] Men with a low baseline TT (<10.4 nmol l^{-1}) had an increased risk of death compared to testosterone levels above these cut-off levels. A significant increased risk of CV mortality was found in men with a TT <8.4 nmol l^{-1} when deaths within the first 6 months were excluded.

Another study evaluated the issue of insulin resistance and looked at diet and exercise program alone versus in combination with TRT in men with type II DM. They reported that a diet and exercise program only resulted in a reduction in HbA1c levels by 0.5% at the end of 1 year, whereas the combination with TRT had a 1.2% reduction.[32]

MORBIDITY AND MORTALITY IN INDUCED ANDROGEN DEFICIENCY

Androgen deprivation therapy (ADT) has been the standard treatment for advanced prostate cancer and induces a profound hypogonadism, with many of these men experiencing changes in body composition such as a decrease in lean muscle mass and an increase in body fat mass.[33] This has been linked to an increased risk of CV events and even sudden death.[34] One of the largest studies to date, where 73,196 men with localized prostate cancer in which one-third were treated with ADT and the rest were not treated and monitored for progression of their disease, were followed for up to 10 years.[35] ADT was associated with an increased risk of incident DM, CHD, MI and sudden death.

In men with DM who were treated with ADT for their prostate cancer, there was an increase in plasminogen activator inhibitor 1 and fibrinogen levels, which suggests the induction of pro-coagulation factors in these patients. These observations strongly suggest that ADT induces metabolic changes that may contribute to the pathophysiology of CVD.[36]

TESTOSTERONE REPLACEMENT THERAPY AND EFFECTS ON MORBIDITY AND MORTALITY

Testosterone replacement therapy is associated with improvements in many domains of sexual function, improvements in bone mineral density, reduced body fat mass, improved muscle mass and strength, and a possible positive effect on lipid levels and glucose control.[1,37] Studies suggest that TRT may even be cardio-protective, where stress test and ST-segment depression is attenuated in men being treated with testosterone, suggesting that TRT may promote vasodilation.[38]

Two studies have now been published directly examining the effect of TRT in men with hypogonadism. The first,[39] analyzed 1031 male veterans greater than 40 years of age who were found to have low testosterone ≤8.7 nmol l^{-1} (250 ng dl^{-1}). They compared survival rates in those who had received TRT and those who had not and found that TRT significantly reduced mortality over a mean follow-up period of 40.5 months. The mortality in men receiving TRT was 10.3% compared with 20.7% in untreated men ($P < 0.0001$). Even after multivariate adjustment, testosterone treatment was associated with a decreased risk of death.

The second study examined retrospectively the effect of TRT for hypogonadism on all-cause mortality in men with type II DM and found significant survival benefits.[31] TRT was associated with a reduced mortality of 8.4% compared to 19.2% in the untreated group. They concluded that testosterone replacement may improve survival in hypogonadal men with type II DM (**Figure 1**).

Treatment with TRT in men with testosterone deficiency showed significant progressive reductions in BMI, weight loss and decreases in waist circumference, which were maintained for at least 30 weeks.[40]

Testosterone replacement therapy and cardiovascular safety

Systematic meta-analyses have not found any adverse effects of testosterone replacement associated with an increase in CV events.[41–43] However, recent reports link TRT to increased CVD and have generated significant debate and controversy over the true impact of testosterone therapy on CVD.

The first of these reports is a retrospective cohort study of men in the Veterans Affairs system in most men with CHD evident

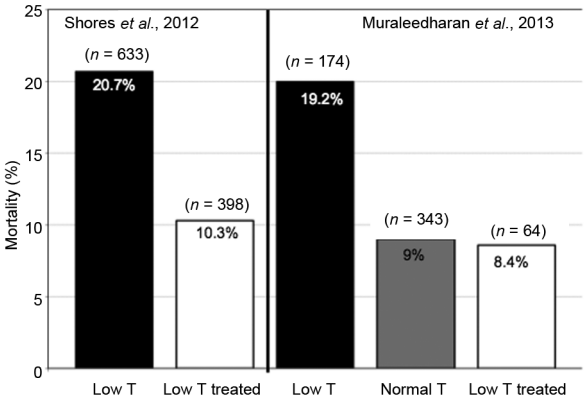

Figure 1: Testosterone deficiency in patients with diabetes is associated with increased mortality.

at angiography.[44] Among men with pretreatment testosterone levels <300 ng dl^{-1}, the authors reported an increased rate of heart attacks, strokes, and deaths in men who received a testosterone prescription compared with men who did not receive a prescription. There were no significant differences in CV events noted for any year of follow-up, however, the overall event curves demonstrate a 29% increase in CV events among men on TRT.

This was a heavily flawed study for many reasons. Firstly, once a subject was started on TRT, it was assumed that treatment continued. In fact, 17.6% had only one prescription. Secondly, no data on the diagnosis of hypogonadism, which should include the presence of symptoms as well as low testosterone levels, were presented. Thirdly, in analyzing this article more closely, raw data showed the percentage of men who suffered a CV event was actually lowered by approximately half for the men receiving TRT compared with the no-testosterone group (10.1% *vs* 21.2%). Statistical analysis using over 50 variables then suggested the opposite result. Furthermore, 1132 subjects with MI or stroke, which were given testosterone after these events, were excluded from the analysis. Without that exclusion, the rate of events in the no–treatment group would have been increased by 71%, critically changing the reported results. Therefore, a safe conclusion cannot be made without providing further statistically significant data addressing the concern that increased testosterone prescriptions results in increased CV events.

As second study, collected data retrospectively from a health-care insurance claims data base following 55,593 prescriptions for testosterone by querying for diagnosis codes, procedure codes, and prescription reports.[45] The authors reported an increased risk of nonfatal MIs in the 3 months after the prescriptions were issued compared to the prior 12 months in these patients and also with a cohort of men treated with phosphodiesterase type 5 inhibitors (PDE5i). Comparing the pre- and post-prescription rates for PDE5i they reports no increase in MI following the issuance of the prescription. Subgroup analysis revealed increased risk of MI with men over the age of 65 years without a prior history of CVD, and for men less than 65 years with a prior history of CVD. They concluded that the risk of MI is substantially increased in older men and in younger men with preexisting, known CVD.

There are several weaknesses in this study with no data on whether or not hypogonadism had been diagnosed or even if the testosterone levels were measured pretreatment, no evidence on if the patients even took the medication, or any evidence to suggest compliance or

monitoring of testosterone levels on treatment, hematocrit, or PSA levels. The risk of MI with testosterone prescriptions was remarkably low. The preprescription rate was 3.48 per 1000 person-years, and the postprescription rate was 4.75 per 1000 person-years. The excess of non-fatal MI was therefore 1.27 events for every 1000 person-years. The difference is clinically insignificant, and unlikely to be reproducible.

Comparison of the MI rates in the PDE5i group is misleading and provides little to no useful information, as these groups are too dissimilar. The authors suggest that the lack of increased MI rate with PDE5i means that the increase in MIs noted with the testosterone prescription group implicates TRT as a CV risk. All of these concerns additively render any conclusions regarding TRT for subgroups questionable and unreliable.

Several other trials have examined the impact of TRT in men with either proven coronary artery disease or moderate chronic heart failure between 3 and 12 months.[38,46,47] The trials have not reported any more CV events compared with the placebo groups, and in fact have overall found benefits. For example, one study reported that testosterone therapy improved functional exercise capacity and VO_{2max} in men with chronic heart failure.[46]

Baillargeon *et al*. investigated 25,420 US Medicare recipients 65 years and older. In this study, a cohort of 6355 men treated with at least one injection of testosterone between January 1, 1997, and December 31, 2005 were matched to 19,065 testosterone nonusers at a 1:3 ratio based on a composite MI prognostic score. A significant trend towards reduced MI rates with T administration was noted with increasing quartiles of risk. For men in the highest prognostic MI risk quartile, treatment with T therapy was associated with significantly reduced risk (hazard ratio = 0.69; 95% confidence interval = 0.53–0.92).[48]

It should be noted that Xu *et al*.[49] published the only one of several prior meta-analyses and systematic reviews to suggest any increased risk with TRT. As with all meta-analyses, the results are influenced greatly by the definitions of endpoints of interest, and the selection of studies. The authors specifically included only studies in which one or more CV events were reported, meaning that studies without any CV events were excluded. This selection process exaggerates the apparent rate of events, and distorts absolute differences in event rates between groups. In addition, just two of the 27 studies contributed 35% of all CV events in the T arm.

The disproportionate influence of these two studies on the outcome of the meta-analysis merits closer scrutiny. One is the study by Basaria *et al*.[50] discussed above, in which 18 of 23 events (incorrectly reported as 25 events by Xu *et al*.) would not normally be included in reporting of CV events. The other is a 1986 Copenhagen study in which a nonapproved oral formulation of micronized testosterone was administered at a remarkably high dose of 600 mg daily to men with cirrhosis of the liver, resulting in serum testosterone concentrations exceeding 4000 ng dl^{-1} (approximately 140 nmol l^{-1}) in a quarter of the testosterone group, and with levels reaching as high as 21,000 ng dl^{-1} (745 nmol l^{-1}), a value approximately 20 times the upper limit of the normal range. Since these oral forms of testosterone are known to cause liver toxicity via a first-pass effect, it should be no surprise that markedly supraphysiologic T doses in a hepatically compromised population would prove harmful. Moreover, the authors appear to have categorized any bleeding event as "CV," including the most frequently observed cause of death in this study, that is, bleeding from esophageal varices. Only 1 MI was noted in the trial. This trial has little relevance to the question at hand: does testosterone repletion cause increased risk of CV events, and its inclusion in a meta-analysis of this type may lead to misleading results.

Recently, Corona *et al*.[51] published a meta-analysis of 75 studies, compared with the 27 analyzed by Xu *et al*. They found no significant association between T therapy and CV events. The results of Xu *et al*. are contradicted by several other meta-analyses, and their results appear due to inclusion of questionable events and studies.

CONCLUSIONS

Testosterone deficiency is associated with a poorer quality of life, reduced physical strength and lean muscle mass, fatigue among many other symptoms and clinical parameters that may lead to earlier mortality. Until date, there has not been a single study that has provided definitive evidence to support the concern that TRT increases CV risk. Contrary to this, most studies noted in this and other reviews suggest that both low endogenous testosterone levels and testosterone deficiency syndrome in men are associated with increased CV risk and events. In addition, TRT appears to decrease this risk, perhaps through modification and improvement of CV risk factors.

AUTHOR CONTRIBUTIONS

KH and MM completed literature search and review, were both involved in drafting the manuscript and critically revising it, and have given final approval of the version to be published.

COMPETING FINANCIAL INTERESTS

KH: no competing financial interests. MM: Consultant for Abbvie and Lipocine.

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