Testosterone Replacement and Cardiovascular Safety: No Straight and Narrow!

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ABSTRACT: The past decade has seen a tremendous increase in the number of men treated for hypogonadism with the expectation of symptomatic benefit. However, the long-term cardiovascular safety of testosterone replacement remains unknown because retrospective studies of testosterone replacement have been inconsistent, and definitive, prospective, randomized studies are lacking. The purpose of this review is to critically appraise the studies on testosterone replacement and cardiovascular outcomes.

KEYWORDS: testosterone, cardiovascular disease, hypogonadism

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Background

The prevalence of hypogonadism in men 45 years or older is 12%–38%,[1,2] and it increases with age, BMI, and in the presence of type 2 diabetes.[3] Longitudinal observational studies show that low testosterone concentration is associated with an increase in the incidence of cardiovascular events.[4–7] Testosterone replacement therapy (TRT) favorably affects the cardio-metabolic profile with improvements in total to HDL cholesterol ratio,[8,9] weight and waist circumference,[8,10] insulin levels,[10] insulin resistance,[9] and C-reactive protein (CRP).[8,10] Serum-free[11] and total[12,13] testosterone levels appear to be inversely related to the carotid intima-media thickness (a surrogate marker for atherosclerosis) with TRT, resulting in a significant decrease in thickness after 12 months of therapy.[14] However, recently published data have posed questions about the cardiovascular safety of TRT in men with hypogonadism. This has garnered the attention of the medical community, media, and general public.

Testosterone and Atherosclerosis

Low concentration of testosterone also appears to be associated with increased atherosclerosis in elderly men (The Rotterdam Study group).[15] Serum-free testosterone concentration is inversely related to presence[11] and mean progression of carotid intima-media thickness of the common carotid artery in men[16] and also with age-adjusted carotid intima-media thickness.[12,13]

Another line of evidence linking low testosterone concentration with cardiovascular disease comes from iatrogenically induced hypogonadism in cases of prostate cancer. Keating and colleagues studied 73,196 men with loco-regional prostate cancer treated with GnRH agonist with follow-up for up to 10 years.[17] Patients with GnRH agonist-induced hypogonadism were more likely to have incident diabetes, coronary heart disease (CAD), myocardial infarction (MI), and sudden cardiac death.

Low Endogenous Testosterone and Mortality

Reduced testosterone concentration is common in elderly men. In 30%–50% of men above 70 years of age, free testosterone concentrations may be low. Low testosterone concentration and hypogonadism have been associated with adverse cardiovascular events and all-cause mortality in longitudinal observational studies of elderly men.[4–7] In one of the earliest studies on this topic, Laughlin et al.[4] prospectively followed 794 men aged 50–91 years (median 73.6) for 20 years in a community setting. The hazard ratio for men in the lowest quartile of testosterone level (<241 mg/dL) was 1.40 for all-cause mortality and 1.38 for cardiovascular mortality. The low testosterone–mortality association was independent of diabetes, metabolic syndrome, and prevalent cardiovascular disease. In a Swedish cohort of a large international study (Osteoporotic Fracture in Men–MrOS),[5] 3014 men with mean age 75 years were followed for 4.5 years. Low free testosterone levels (comparison of quartile 1 with quartiles 2–4) were associated with 65% increased risk of mortality. Yeap et al.[6] studied 3443 men aged over 70 years with median

follow-up of 3.5 years. After adjusting for confounding factors (including waist to hip ratio, waist circumference, smoking, hypertension, dyslipidemia), total and free testosterone in the lowest quartile predicted increased incidence of stroke or transient ischemic attack (TIA) [total testosterone hazard ratio (HR) = 1.99; 95% CI 1.33–2.99 and free testosterone hazard ratio = 1.69; 95% CI 1.15–2.48]. In a more recent study, Yeap et al found that elderly men with testosterone concentration, between 283 and 453 ng/dL, had the lower all-cause mortality as compared to men with testosterone concentrations higher and lower than this "optimal range".[18] Haring and colleagues[19] followed 1954 men prospectively for an average of 7.2 years. Men with low serum testosterone (<250 ng/dL) had a significantly higher mortality from all causes (HR 2.32; 95% CI 1.38–3.89) and cardiovascular disease (HR 2.56; 95% CI 1.15–6.52). Similarly, Hyde and colleagues[20] followed 3637 community-dwelling men for a mean period of 5.1 years with lower free testosterone, predicting higher cardio vascular disease (CVD) mortality. There are also smaller case–control, cross-sectional, and retrospective studies that have also demonstrated an association of low testosterone with increased mortality.[21–23] On the other hand, at least two longitudinal studies did not demonstrate a relationship between low testosterone and cardiovascular mortality.[24,25] These studies were performed on a much younger population (mean ages, 52 and 55 years). The lack of association may possibly be explained by the fact that these studies were underpowered due to very low mortality rates.

The available data suggest that the cause of low testosterone in elderly men is the accumulation of comorbidities with age. Healthy aged men have minimal or no decline in testosterone concentration. Studies have evaluated the association of mortality with low testosterone in men with diabetes or CAD. Ponikowska et al.[26] followed 153 men with stable CAD and type 2 diabetes, and found that subnormal total testosterone levels were associated with 139% increased cardiovascular mortality when followed over a mean duration of 24 months of TRT. Similar findings were reported by Malkin et al.[7] Men with CAD and a low testosterone level (n = 930) at baseline had 127% excess risk for cardiovascular mortality when followed for a mean duration of 6.9 years. In contrast, a case–control study[27] of 163 men who experienced a fatal or nonfatal MI as compared with 163 matched controls revealed no differences in the total or free testosterone levels in the two groups. A study of 581 men with type 2 diabetes (238 with subnormal testosterone and 343 with normal total testosterone concentration) found total mortality rates of 17% and 9% in men with subnormal and normal testosterone concentrations, respectively (multivariate adjusted HR of 2.02).[28]

Given the strength of association of low testosterone concentration with mortality, it is not surprising that meta-analyses have also confirmed this association. An analysis by Araujo et al.[29] included 11 studies of all-cause mortality (16,184 patients) with 7 studies of CV mortality (11,831 patients). Low endogenous testosterone levels were associated with increased risk of CV and all-cause mortality; however, there was significant between-study heterogeneity. A recently published meta-analysis[30] that included 70 studies (both cross-sectional and longitudinal) also related low testosterone concentration with increased risk of cardiovascular disease and cardiovascular mortality.

Although the epidemiological data demonstrate that low endogenous testosterone concentrations in men are associated with an increased risk of CVD, it is not known whether low testosterone is merely a marker of increased risk or contributes to the cause. Thus, these observations do not demonstrate that testosterone supplementation will reduce cardiovascular risk or even that it is safe.

TRT and Cardio-Metabolic Risk Profile

Researchers used to believe that testosterone treatment adversely affects cardiovascular risk because it lowers high-density lipoprotein (HDL) cholesterol concentration. However, that effect is restricted to treatment that achieves supranormal concentrations of testosterone (eg, during abuse of androgens for body building). Testosterone has not been shown to cause any meaningful change in HDL concentrations[31] in studies where testosterone is replaced to normal levels, while many cardiovascular risk factors change favorably. The TIMES2 study investigated the effects of TRT in 220 men with hypogonadism with type 2 diabetes and/or metabolic syndrome in a multicenter, randomized, double-blind, placebo-controlled study.[9] TRT improved insulin resistance, total and LDL cholesterol, Lp(a), body fat composition, and sexual health over a 6-month period. Haider and colleagues analyzed data from observational prospective registries for 156 obese, diabetic men on long-term TRT for hypogonadism. TRT in these individuals resulted in significant and sustained improvements in weight, waist circumference, HbA1c, total cholesterol to HDL ratio, and CRP.[32] In a registry of seven general practices that provided TRT (long-acting testosterone undecanoate) for 30 weeks in a double-blind placebo fashion to 211 men with type 2 diabetes, TRT significantly improved HbA1c, total cholesterol, waist circumference, quality of life, and sexual function. The improvements were dependent upon achieving adequate testosterone concentrations but less marked in those with depression at baseline.[33–35] Kalinchenko et al.[10] studied 184 men with hypogonadism and metabolic syndrome to receive placebo or parenteral TRT. After 30 weeks of randomization, TRT recipients had significant decreases in weight, waist circumference, insulin levels, and CRP. Francomano et al, in a prospective case–control study, demonstrated that TRT in patients with hypogonadism resulted in improvement of obesity, blood pressure, glycemic control, and bone mineral density.[36] Aversa and colleagues[14] demonstrated a significant decrease in carotid intima-media thickness after 12 months of parenteral TRT in a random-

ized, placebo-controlled trial in men with hypogonadism with metabolic syndrome.

TRT and Cardiovascular Outcomes

No randomized control trials (RCTs) have been conducted to examine the question: "Does TRT change cardiovascular outcomes in men?" Cardiovascular outcomes have been sporadically reported in randomized trials of TRT designed for other endpoints (such as muscle strength, glucose control, etc.), but these trials were underpowered to look at cardiac events. In the absence of robust RCTs examining the effects of TRT on long-term cardiovascular outcomes, we have to rely on currently available research. While most of the published data do not reveal an increase in MACE (major adverse cardiac event), there have been recent reports to the contrary. The following paragraphs describe the trials (prospective and retrospective) and the meta-analysis that have reported cardiovascular events after TRT.

Randomized Control Trials

In the Testosterone in Older Men with Mobility Limitations trial, 209 frail elderly (mean age of 74) men with low total serum testosterone levels and high prevalence of comorbidities were randomly assigned a placebo gel or testosterone gel, to be applied daily for 6 months.[37] The trial, which was designed to determine the effects of TRT on leg strength and physical function, was halted for concerns about increased cardiovascular-"like" events (including pedal edema, which would be expected with TRT in elderly population) in the treatment group. The authors concluded that the small number and diverse adverse outcomes of variable clinical significance may have been due to chance alone. Similar investigations in elderly population assessing effects of TRT on physical function, body composition, quality of life, and other outcomes have not raised such concerns.[38–40] Trials in other populations with high cardiovascular risk (such as type 2 diabetes) have also not shown a change in rates of cardiovascular events with TRT.[9,41]

Retrospective Studies

Shores and colleagues studied middle aged and elderly veterans with hypogonadism. They compared the total mortality rates in persons on TRT ($n = 398$) and those not on TRT ($n = 633$). In this cohort, TRT was associated with decreased mortality over the average follow-up time of more than 3 years. This effect persisted after adjustments for age and other comorbidities.[42] Retrospective assessment of the effect of TRT on mortality in a cohort of men with hypogonadism and type 2 diabetes replicated the above findings. TRT ($n = 64$) was associated with reduced mortality (8.4%) as compared to 19.2% in the untreated group ($n = 174$).[28] A retrospective claims-based analysis of a 5% sample of Medicare beneficiaries by Baillargeon et al compared 6,355 men aged 66 years or older who received intramuscular TRT and compared them to 19,065 who did not. TRT was not associated with an increased risk of MI (HR = 0.84; 95% CI = 0.69–1.02). Interestingly, TRT seemed to have a protective effect in men at highest risk of MI (HR = 0.69; 95% CI = 0.53–0.92).[8]

In contrast to the above, two groups have reported the association of TRT with adverse cardiovascular outcomes.[43,44] Vigen et al examined a composite outcome of all-cause mortality, MI, and stroke rates in a cohort of men with low testosterone levels who had undergone coronary angiography and subsequently received TRT. The actual reported rate of events was 10.1% for the testosterone-treated group, and 21.2% for controls, showing a reduced event rate in the treated group by more than half. However, after statistical adjustment for over 50 variables, the outcome was reversed! The use of TRT was associated with increased risk of adverse outcomes (19.9% in no treatment group vs 25.7% in treated group) 3 years after the angiography. The study has been criticized for its statistical techniques, lack of adjustment for baseline testosterone concentrations, and inadequacy of testosterone treatment in study subjects, and some corrections in actual data have been published by the authors. However, the likely explanation for the stark difference between adjusted and actual event rates is probably that the actual effect size of TRT on study points was much smaller than the effect of comorbidities that needed adjustment among mismatched groups. In another study, Finkle and colleagues examined 55,593 insurance claims and compared the incidence of rate of MI in the one year prior and 90 days after initial prescription of TRT. They reported an increased rate of nonfatal MIs especially in men aged 65 or older. In men younger than 65 years, the risk was confined to those with preexisting heart disease. There was no control group. The strategy of comparison of pre- and post-prescription event rates is fraught with confounders. Most practitioners prescribe TRT to increase libido and energy levels in men. Diagnosing hypogonadism and prescribing TRT is usually a low priority in a man with recent MI. Thus, it would be expected that the pre-prescription period would selectively include men without a history of MI, resulting in falsely low rates. The increase in MI over the duration of the study can be partially explained by the continuing accumulation of events in a "high cardiovascular risk" population. In fact, the event rates in the study were approximately one-third of what would be expected in a group of men with mean age of 54 years (average age of study participants).[45,46] There was no information available on testosterone concentrations (pre or post treatment) or of cardiovascular risk factors in subjects who were treated. Furthermore, the treatment duration of 3 months is wholly inadequate for a trial looking at cardiac events. This is in contrast to the above-mentioned insurance-claims-based analysis by Baillargeon et al.[8]

Meta-Analyses

Multiple meta-analyses have evaluated the effect of TRT on cardiovascular events.[31,47–50] A recent meta-analysis by

Corona and colleagues, included 75 randomized placebo-controlled trials of TRT, evaluated the incidence of MACE where available.[50] They reported no association between the TRT and placebo groups even after accounting for variables such as funding source, age at treatment, and other chronic diseases. This lack of association between cardiovascular events and TRT concurs with the results of all the other meta-analyses except the one by Xu et al.[49] They report that TRT increased the cardiovascular-related event risk in studies not funded by pharmaceutical companies. The data available from six RCTs[51–55] with cardiovascular outcomes were analyzed by Corona et al.[30] These were heterogeneous trials with patients with preexisting coronary heart disease (CHD), which enrolled 258 patients and showed improvements in exercise capabilities (significant increase in treadmill test duration and time to 1-mm ST segment depression). These trials enrolled persons with varying basal T rates, and used different T supplements.

The U.S. Food Drug Administration (FDA) in its recent denial of the citizen petition to make changes to the safety labeling of TRT provides a detailed analysis of methodological deficiencies of all the studies that show association with adverse cardiovascular events.[56] The Testosterone Trial, funded by the National Institutes of Health (NIH), will test the hypothesis that testosterone treatment in men older than 65 and unequivocally low serum testosterone concentration compared to placebo treatment will improve their physical function, sexual function, vitality, cognitive function, and low hemoglobin concentration, and decrease risk factors for CVD and diabetes. The results of this study will add to our understanding of TRT. However, it is not powered to provide data that will resolve the controversy of TRT and cardiovascular outcomes.[57]

Conclusion

Epidemiological data show an association of hypogonadism and decreased survival. It seems intuitive, then, that TRT in men with hypogonadism would lead to improved cardiovascular outcomes. However data on this are a mixed bag. Low testosterone concentrations may merely be a marker of a chronic systemic inflammatory state involving the hypothalamic–pituitary–gonadal axis rather than the agent modulating adverse cardiovascular outcomes. TRT is beneficial for patients suffering from symptoms of hypogonadism and probably is safe for use based on current evidence. TRT should be initiated in appropriate patients, maintained, and monitored subsequently using standardized plans.[58] Further research should be conducted to understand the effect of TRT on mechanisms that underlie atherosclerosis and cardiovascular events. Appropriately powered trials of TRT that evaluate MACE should be carried out in "at-risk populations", such as type 2 diabetes and metabolic syndrome. If these trials show a benefit of TRT on MACE, then it is likely that a large trial on TRT and elderly men with MACE reduction as primary endpoint would be funded.

Author Contributions

Analyzed the data: SH, SD, RC. Wrote the first draft of the manuscript: SH, RC. Contributed to the writing of the manuscript: SD. Agree with manuscript results and conclusions: SH, SD, RC. Jointly developed the structure and arguments for the paper: SH, SD. Made critical revisions and approved final version: SH, SD, RC. All authors reviewed and approved of the final manuscript.

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