Safety of Testosterone Therapy in Cardiovascular Disease: Where are we now?

Alistair J. Aaronson, MD, Ryan P. Morrissey, MD, Robert Willix, MD, Cam T. Nguyen, MD,

Ernst R. Schwarz, MD, PhD

Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA,

Cenegenics Medical Institute, Las Vegas, NV,

USA

Word Count: 2888

References: 37

Short Title: testosterone safety

No disclosures.

Corresponding Author:

Ernst R Schwarz, MD, PhD, FACC, FAHA, FESC

8700 Beverly Boulevard, Suite 6215

Los Angeles, CA 90048

Tel: (310) 423 1876

Fax: (310) 423 1498

Email: ernst.schwarz@cshs.org

ABSTRACT

Testosterone has been used for decades in the treatment of men with hypogonadism, of females with low libido, and more recently in patient populations with cardiac disease, in particular patients with heart failure. The benefits of testosterone supplementation have been demonstrated in the literature, but there is also concern that testosterone supplementation may not be benign, especially when administered to achieve supraphysiological levels, as frequently practiced in abusing athletes. This review seeks to address the link between testosterone levels and cardiac disease while discussing the safety concerns of testosterone supplementation in clinical practice. Ultimately, the definitive role of testosterone in cardiovascular disease remains contentious, but may have niche roles in certain conditions such as advanced heart failure or cardiac cachexia.

Key words: Testosterone, Cardiovascular Disease, Coronary Heart Disease, Hypogonadism, Dyslipidemia, Heart Failure.

INTRODUCTION

Testosterone has been used for decades in the treatment of male hypoganadism as well as in women with low libido, and more recently as an adjunctive treatment in populations of patients with cardiac disease. Low testosterone levels have been linked to heart disease as well as risk factors for heart disease, and testosterone supplementation in some studies has been associated with improved cardiovascular outcomes. However, there has been concern that the clinical use of testosterone may be potentially unsafe, which is mainly based on reports of abuse of steroid use among some athletes in order to achieve supra-physiological levels to gain improved muscle strength and physical performance. In this review, the authors seek to specifically clarify the ambiguous role testosterone has hitherto played in cardiovascular health, especially with regard to its safety in clinical use. While testosterone has been shown to have potential deleterious physiological cardiovascular effects, there is mounting evidence to support that testosterone has the ability to promote and improve cardiovascular health when administered to maintain physiological levels.

CARDIOVASCULAR EFFECTS OF LOW TESTOSTERONE

The detrimental cardiovascular effect of low circulating testosterone has been demonstrated in both animal models and clinical trials, with androgen deficiency being repeatedly associated with such cardiovascular risk factors as metabolic syndrome, obesity, diabetes type II (1), hypertension, and dyslipidemia (2). Evidence for such metabolic derangements comes primarily from trials in which patients received androgen deprivation therapy, a modality that is often used in the treatment of prostate

cancer. In patients undergoing androgen deprivation therapy status post radical prostatectomy for prostate cancer, patients had an increased incidence of metabolic syndrome and diabetes type II, as well as elevated triglycerides, total cholesterol, and low density lipoprotein (LDL) levels when compared to the levels prior to therapy (3). In a study of 171 males with coronary risk factors but no frank disease, a 77-month follow up revealed 20 cardiovascular events. Subjects in the lowest tertile of testosterone levels had a 4-fold cardiovascular event risk compared those in the highest tertile (4).

In addition to being linked to the development of atherosclerosis by causing dyslipidemia(5), low testosterone levels have also been associated with increased incidence of atherosclerosis. In a cohort of 90 men, 60 with positive coronary angiograms and 30 with negative coronary angiograms, those with documented coronary artery disease (CAD) demonstrated significantly lower levels of testosterone than patients without coronary artery disease, as documented by coronary angiography (6). Sieminska et al. studied 105 men with angiographically-documented coronary artery disease and reported significantly lower levels of free testosterone in CAD patients compared to controls (7).

Regarding mortality, Haring et al. demonstrated that among 1954 men who were recruited for the prospective population-based Study of Health in Pomerania, all-cause mortality and cardiovascular mortality both were significantly increased in individuals with lower serum testosterone levels (8). Malkin et al. corroborated such findings in a longitudinal follow up study of 930 consecutive men with CAD. Patients were divided according to testosterone levels. At seven years testosterone deficient patients had a 21% all-cause mortality compared to a 12% mortality in patients with normal

testosterone levels (9). In addition, in a study of 3262 patients undergoing radical prostatectomy, the 1015 patients receiving androgen deprivation therapy had a 5.5% cardiovascular mortality at 5 years compared to a 2% mortality rate in patients who did not receive androgen deprivation therapy (10).

While low testosterone states have been correlated with increased cardiovascular risk factors, disease, and mortality, several studies showed that testosterone might be unrelated to the occurrence of CAD in men. Barrett-Connor et al. published a prospective study of 1009 men aged 40-79 who were followed over 12 years. No correlation between sex hormones and cardiovascular disease was found (11). Yarnell et al. studied 2,512 men aged 45-59 over 5 years for associations between testosterone levels and ischemic heart disease. Of 153 patients who developed ischemic heart disease (both nonfatal and fatal), there was no significant difference in testosterone levels in those with ischemic heart disease compared to men without CAD. Of interest, the authors showed that patients with lower testosterone levels demonstrated higher triglycerides and decreased high density lipoprotein (HDL) levels (12).

EFFICACY OF TESTOSTERONE REPLACEMENT

A meta-analysis of 29 randomized controlled trials that included 1083 middle-aged men with low testosterone (13) showed that restorative testosterone therapy to physiological levels improved bone mineral density at the lumbar spine, strength of leg/knee extension and hand grip strength, and decreased total body fat while reducing total cholesterol. Those patients with lower baseline testosterone concentrations had

the greatest effect when treated with testosterone. No serious adverse events during testosterone therapy were noted in this meta-analysis. In a randomized, double-blind, placebo-controlled study of 50 hypogonadal men with metabolic syndrome who were treated with testosterone, there was a marked decrease in metabolic syndrome after treatment. No significant adverse events in the treatment group were noted (14).

In addition to decreasing cardiovascular risk factors such as cholesterol and metabolic syndrome, testosterone replacement has also been shown to increase HDL, which is known to be athero-protective by removing lipids from developing fatty streaks, the precursor structures to frank atherosclerosis (5). An animal study by Nettleship et al. showed that physiological testosterone replacement in testicular feminized mice both increased HDL levels and actually inhibited fatty streak formation in the mouse aortas (15). Others studies have corroborated such HDL-increasing results, while some others showed no testosterone effect on HDL (16). In summary, the effects of testosterone on HDL levels are controversial and still uncertain.

More recently, a double-blind placebo-controlled clinical trial reported that in 184 men with metabolic syndrome and hypogonadism, a 30-week trial of parenteral testosterone therapy resulted in significant decreases in weight, BMI, waist circumference, insulin levels, as well as pro-inflammatory markers associated with heart disease such as IL-1-beta, TNF-alpha, and CRP. Of note, lipid profile changes were not significant, nor were Il-6 or Il-10 level changes (17). Gruenewald et al. also demonstrated that testosterone treatment consistently led to improved bone mineral density, strength, libido, and erectile function. In men with CAD, the authors demonstrated reduced exercise-induced myocardial ischemia and improved symptoms.

However, both hematocrit and prostate specific antigen (PSA) levels were noted to be frequently increased in men treated with testosterone (18).

In a randomized, double-blinded, placebo-controlled study of 46 men with stable angina, half were given 5mg testosterone transdermal patch and half placebo over 12 weeks, and time to 1-mm-ST-segment depression was assessed as a surrogate for exercise-induced myocardial ischemia. There was a statistically significant improvement in ST-segment depression time in the testosterone treated group, indicating a reduction in exercise-induced ischemia in men with angina who were treated with low doses of testosterone. No significant changes in PSA, lipids, or hematocrit were detected during the study (19). A randomized, double-blinded study of 50 men with ST depressions after a modified two-step exercise test found that after 8 weeks, those treated with weekly injections of testosterone cypionate had a 51% decrease in depression in the summation of leads II, V4, V5, V6. Again, this indicates that testosterone may play a role in diminishing exercise-induced ischemia in men with known CAD (20).

Testosterone therapy has also proven efficacious in the treatment of heart failure and cardiac cachexia, a state of severe end-stage heart failure hallmarked by muscle wasting, increased catabolism with high levels of TNF-alpha, and decreased anabolism with low levels of growth hormone and testosterone (21). **ADD CAMICI study here** !!!!!!!!!!!!In addition, in a recently published study of 36 elderly women with heart failure and an average ejection fraction (EF) of 32.9% on maximal medical therapy, supplemental transdermal testosterone supplementation resulted in significant

improvements in 6-minute walk tests, with an average improvement of 36.4 +/- 11.9 meters. Of note, those women with lower baseline testosterone levels had a more marked response than those with normal levels at initiation of therapy (125.2 +/- 60.3 meters versus 68.8 +/- 53.1 meters) (22). No significant change in EF was noted. In a study of 76 men with heart failure with average baseline EF 32.5%, functional capacity was improved by measure of 6-minute walk test. No significant changes in EF were noted, but there was a decrease in heart failure symptoms in the testosterone treatment group compared to the placebo group as assessed by an average decrease of one NYHA class (23).

SAFETY OF TESTOSTERONE REPLACEMENT

While promising as a potential adjunctive therapy in the prevention or treatment of cardiac disease, it is crucial to tread carefully with regard to any treatment that may have potentially deleterious effects. Testosterone therapy has been linked to exacerbation of prostate cancer (24) and to an increase in prostate specific antigen and hematocrit (18).

A laboratory study on human umbilical vein endothelial cells demonstrated that testosterone exposure increases early stages of apoptosis in endothelial cells compared to controls at 48 hours, signaling a potentially deleterious effect on vasculature (25). However, it should be noted that testosterone levels used in this experiment were supraphysiologic, and the time course of the study was only 48 hours, so one cannot make direct implications about physiological testosterone supplementation over the long-term.

In addition, some trials have raised concerns that testosterone treatment can lead to the development of ventricular hypertrophy and deterioration of left ventricular function (26) as well as to increased LDLs, decreased HDLs, and an increased frequency of myocardial infarctions (27). Of note, these cardiac effects were demonstrated in anabolic steroid users, with testosterone administration being significantly supraphysiologic **(be specific here, what levels???)**. In contrast, when administered in testosterone deficient patients to only reach physiological levels, testosterone has been shown to decrease ventricular mass and increase cardiac index while improving lipid profiles (23,28).

Several large studies that examined the efficacy of testosterone treatment have shown potential safety hazards in the use of testosterone. Dean et al. studied the effects of testosterone gel in 371 hypogonadal men over a 12 month time period. Restoring testosterone to physiological levels resulted in an increased bone mineral density, increased lean muscle mass, decreased fat percentage, improved sexual function, and improved mood. However, among those 371 men, 40 reported “adverse events” that warranted drug discontinuation. The four most common adverse events in descending order were elevated PSA, elevated hematocrit, elevated hemoglobin, and application site erythema. The average baseline entrance PSA was 1.26 ± 0.005ng/mL, and average PSA at 12 months was increased by 0.45ng/mL.Three patients were diagnosed with prostate cancer. Hemoglobin and hematocrit also increased, with average increases of hemoglobin by 1 g/dl and an average increase of hematocrit by 3 percentage points (29).

Wang et al. studied 163 hypogonadal men receiving Androgel™, another testosterone gel preparation. Average baseline entrance PSA was 0.85 ± 0.06ng/mL, and average PSA at 6 months of treatment was 1.11 ± 0.08ng/mL. Six subjects attained PSA levels above the predetermined study threshold of 5.5ng/mL, at which time the gel was discontinued. Three subjects had biopsy shown prostate cancer. Of note, this study was not placebo controlled, nor powered to determine prostate cancer risk in testosterone treated patients. Hemoglobin and hematrocrit also increased, in a dose dependent manner, with 14 subjects at one time or another during the trial having hemoglobin levels greater than 18 g/dL, at which point the gel was either reduced in dosage or discontinued. Other adverse events noted during the time course of this trial were acne (7%, n=12), application site erythema (7%, n=12), transurethral resection of prostate in one subject for lower urinary tract symptoms, and deep vein thrombosis in one subject (30).

A recent trial raised concerns regarding the safety of testosterone administration by demonstrating an increase in adverse “cardiovascular-related events” in the testosterone treatment group (n=23) compared to placebo (n=5), prompting an early cessation of the study at the recommendation of the data and safety monitoring board (31). Of interest, in this particular study, the testosterone group had a higher incidence of hyperlipidemia and “pre-existing cardiovascular disease” at baseline compared to the control group, so the results in this group may in fact have been confounded by baseline elevated lipids and pre-existing cardiovascular disease rather than solely testosterone administration. Also, the testosterone group received supraphysiological levels of testosterone (31). The definition of “cardiovascular-related events” was also defined

quite broadly in this study, with the most common event in the testosterone group being peripheral edema (n=5), as defined by clinical exam, without echocardiographic or catheterization findings to link this finding to a cardiac etiology. Although there were two myocardial infarctions in the testosterone group (versus none in the placebo arm), these numbers are far too small to make meaningful conclusions(31).

Lastly, the study population included hypogonadal men over the age of 65 with severely limited mobility and chronic medical conditions, with those under the age of 65 and those with severe hypogonadism being excluded (31). Therefore, the results of this study do not imply that testosterone administration at physiological doses is unsafe outside of this narrow niche population.

By far the greatest proportion of literature focuses on the testosterone treatment for the hypogonadal male. However, women have also been treated with testosterone and the safety of use in women should also be explored. The most likely side effects in women treated with testosterone are hirsuitism and acne (32), as well as virilization in the form of deepening of the voice and clitoromegaly (33), but most of these effects are seen when testosterone is administered in supraphysiological doses (34).

Far more rare, and more of a safety concern in women being treated with testosterone, is the potential for increased breast cancer risk. A prospective case-control study of 266 premenopausal women found that the relative odds for developing breast cancer was 4.2 in the women with highest quartile of bioavailable testosterone, inferring that higher testosterone levels in women may incur increased risk of developing breast cancer (35). Other studies, however, have shown that increased

testosterone levels in women were not associated with increased risk of breast cancer. Traish et al. reviewed female-to-male transsexuals treated with testosterone and found that in those treated with supraphysiological levels of testosterone in their transformation, there was no increase in vascular disease, breast cancer, or mortality (36).

In June 2010, The Endocrine Society Task Force published the guidelines to ensure safety of testosterone administration in hypogonadal men. The society's recommendation is to use testosterone therapy in "men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density." Target testosterone level should be in the mid-to-normal range. However, testosterone treatment is not recommended for patients with "breast or prostate cancer, a palpable prostate nodule, PSA greater than 4ng/mL or 3ng/mL in men at high risk for prostate cancer, hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms with an International Prostate Symptom Score above 19, or uncontrolled or poorly controlled heart failure" (37).

DISCUSSION

Low testosterone has been associated with cardiovascular risk factors, cardiovascular disease, and mortality, and testosterone replacement therapy has been demonstrated in the literature to be effective in minimizing cardiovascular risk factors and improving cardiovascular outcomes in individuals both with and without underlying cardiovascular disease. The beneficial effects have primarily been found in

hypogonadal men, but also in women being treated with testosterone for low libido. However, the use of testosterone in the clinical setting has been associated in some studies with adverse safety outcomes such as depressed ventricular function and myocardial infarction. It should be noted that these safety concerns were primarily described when the doses of administered testosterone were supraphysiologic, such as in anabolic steroid users; however some adverse events have also been described at physiological levels.

EXPERT OPINION

The safety concerns of testosterone administration are exacerbation of prostate cancer, breast cancer, and elevation of prostate specific antigen and hematocrit levels with its potential clinical sequelae. Therefore guidelines have been recommended to discourage the use of testosterone in susceptible populations. However, cardiovascular safety concerns have more often been documented in the literature when testosterone is administered at supraphysiologic doses, such as in anabolic steroid users or in clinical trials and animal models in which supraphysiologic doses were used. The benefits of testosterone administration in men with low testosterone, in order to restore physiologic levels of testosterone, has been associated with improvements in surrogates of cardiovascular health such as fat percentage, metabolic syndrome, lipid profiles, and cardiac index. It also appears that when the baseline testosterone level is lower, restorative testosterone therapy to physiological levels becomes more beneficial.

Testosterone can be used in patients with cardiovascular disease when the achieved levels are physiological rather than supraphysiological: in particular, in our

own population of pateitns with advanced stages of heart failure we have had excellent success in providing testosterone therapy in particular in those with cardiac cachexia. More clinical studies are warranted to further elucidate testosterone's role in cardiovascular disease prevention and treatment. Also, very few data are available in women. **So summarize here: When to use testosterone, which populations, importance of monitoring and follow up, selction of pts, etc.. !!!**

References

1. Zitzmann M. Testosterone deficiency, insulin resistance and the metabolic syndrome. Nat Rev Endocrinol 2009;5:673-81.
2. Jones TH. Testosterone deficiency: a risk factor for cardiovascular disease? Trends Endocrinol Metab 2010;21:496-503.
3. Kintzel PE, Chase SL, Schultz LM, O'Rourke TJ. Increased risk of metabolic syndrome, diabetes mellitus, and cardiovascular disease in men receiving androgen deprivation therapy for prostate cancer. Pharmacotherapy 2008;28:1511-22.
4. Akishita M, Hashimoto M, Ohike Y, et al. Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. Atherosclerosis 2009;210:232-6.
5. Traish AM, Abdou R, Kypreos KE. Androgen deficiency and atherosclerosis: The lipid link. Vascul Pharmacol 2009;51:303-13.
6. English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. Eur Heart J 2000;21:890-4.
7. Sieminska L, Wojciechowska C, Swietochowska E, et al. Serum free testosterone in men with coronary artery atherosclerosis. Med Sci Monit 2003;9:CR162-6.
8. Haring R, Volzke H, Steveling A, et al. Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79. Eur Heart J 2010;31:1494-501.

9. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Low serum testosterone and increased mortality in men with coronary heart disease. Heart 2010;96:1821-5.
10. Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 2007;99:1516-24.
11. Barrett-Connor E, Khaw KT. Endogenous sex hormones and cardiovascular disease in men. A prospective population-based study. Circulation 1988;78:539-45.
12. Yarnell JW, Beswick AD, Sweetnam PM, Riad-Fahmy D. Endogenous sex hormones and ischemic heart disease in men. The Caerphilly prospective study. Arterioscler Thromb 1993;13:517-20.
13. Isidori AM, Giannetta E, Greco EA, et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf) 2005;63:280-93.
14. Aversa A, Bruzziches R, Francomano D, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. J Sex Med 2010;7:3495-503.
15. Nettleship JE, Jones TH, Channer KS, Jones RD. Physiological testosterone replacement therapy attenuates fatty streak formation and improves high-density

lipoprotein cholesterol in the Tfm mouse: an effect that is independent of the classic androgen receptor. Circulation 2007;116:2427-34.

16. Shabsigh R, Katz M, Yan G, Makhsida N. Cardiovascular issues in hypogonadism and testosterone therapy. Am J Cardiol 2005;96:67M-72M.

17. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol (Oxf) 2010;73:602-12.

18. Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. J Am Geriatr Soc 2003;51:101-15; discussion 115.

19. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. Circulation 2000;102:1906-11.

20. Jaffe MD. Effect of testosterone cypionate on postexercise ST segment depression. Br Heart J 1977;39:1217-22.

21. Anker SD, Chua TP, Ponikowski P, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 1997;96:526-34.

22. Iellamo F, Volterrani M, Caminiti G, et al. Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study. J Am Coll Cardiol;56:1310-6.

23. Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH, Channer KS. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. Eur Heart J 2006;27:57-64.
24. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996;88:1118-26.
25. Ling S, Dai A, Williams MR, et al. Testosterone (T) enhances apoptosis-related damage in human vascular endothelial cells. Endocrinology 2002;143:1119-25.
26. Sullivan ML, Martinez CM, Gennis P, Gallagher EJ. The cardiac toxicity of anabolic steroids. Prog Cardiovasc Dis 1998;41:1-15.
27. Achar S, Rostamian A, Narayan SM. Cardiac and metabolic effects of anabolic-androgenic steroid abuse on lipids, blood pressure, left ventricular dimensions, and rhythm. Am J Cardiol 2010;106:893-901.
28. Pugh PJ, Jones TH, Channer KS. Acute haemodynamic effects of testosterone in men with chronic heart failure. Eur Heart J 2003;24:909-15.
29. Dean JD, Carnegie C, Rodzvilla J, Smith T. Long-term effects of testim(r) 1% testosterone gel in hypogonadal men. Rev Urol 2004;6 Suppl 6:S22-9.
30. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab 2004;89:2085-98.
31. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109-22.

32. Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 2008;359:2005-17.

33. Basaria S, Dobs AS. Safety and adverse effects of androgens: how to counsel patients. Mayo Clin Proc 2004;79:S25-32.

34. Shufelt CL, Braunstein GD. Safety of testosterone use in women. Maturitas 2009;63:63-6.

35. Dorgan JF, Stanczyk FZ, Kahle LL, Brinton LA. Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk. Breast Cancer Res 2010;12:R98.

36. Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female-to-male transsexuals (FMT) treated with pharmacological testosterone therapy. J Sex Med 2010;7:3758-64.

37. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536-59.