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REVIEW

Testosterone and Cardiovascular Health

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Abstract

There is an ongoing debate in the medical community regarding the effects of testosterone on cardiovascular (CV) health. For decades, there has been conflicting evidence regarding the association of endogenous testosterone levels and CV disease (CVD) events that has resulted in much debate and confusion among health care providers and patients alike. Testosterone therapy has become increasingly widespread, and after the emergence of studies that reported increased CVD events in patients receiving testosterone therapy, the US Food and Drug Administration (FDA) released a warning statement about testosterone and its potential risk regarding CV health. Some of these studies were later found to be critically flawed, and some experts, including the American Association of Clinical Endocrinologists and an expert panel regarding testosterone deficiency and its treatment, reported that some of the FDA statements regarding testosterone therapy were lacking scientific evidence. This article summarizes the current evidence regarding the relationship between testosterone (endogenous and supplemental) and CV health. A literature review was conducted via search using PubMed and specific journal databases, including the *New England Journal of Medicine* and the *Journal of the American College of Cardiology*. Key search terms included *testosterone and cardiovascular health*, *coronary artery disease*, *heart failure*, *androgen deprivation therapy*, *intima-media thickness*, and *adrenal androgens*. Initial study selection was limited to publications within the past 10 years (January 1, 2007, through December 31, 2016); however, key publications outside of this time frame were selected if they provided important quantitative data or historical perspectives for the review of this topic. The search was further supplemented by reviewing references in selected articles.

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There is an ongoing debate in the medical community regarding the effects of testosterone on cardiovascular (CV) health. The combination of the male preponderance of coronary artery disease (CAD), the protective effects of estrogen in premenopausal women, and the increased incidence of CV disease (CVD) death in men abusing anabolic steroids led to the belief that testosterone is deleterious to the male heart.[1] Contrary to this view, there is mounting evidence that normal physiologic levels of testosterone are beneficial to the male CV system and that testosterone deficiency is associated with an unfavorable metabolic profile, including increased adiposity, insulin resistance, diabetes, and adverse CVD events, such as myocardial infarction (MI) and mortality.[2-12] Despite the recurrence of these trends in the literature, no causal association has been proved, and results have been conflicting.

Androgen deprivation therapy (ADT) in patients with prostate cancer has been studied in an attempt to identify an association between testosterone depletion and increased CVD events, which would possibly suggest a causal link between testosterone deficiency and CVD events. The effects of testosterone replacement therapy on CV health has also been intensely scrutinized, with mixed results in the literature. There are multiple reasons for the controversy regarding this therapy, including variability in study designs, variability in definitions of CVD events, and underpowered studies that are unable to draw conclusions about various study outcomes. Also, the Food and Drug Administration (FDA) issued a safety warning regarding the use of testosterone-containing products due to a potential risk of CV harm after the release of studies that reported increased CVD events in patients receiving testosterone therapy, which were later found to be critically flawed. Some experts felt that aspects of the FDA position on testosterone therapy were lacking scientific evidence.[6,13] The aim of this report is to explain the controversy and clarify what the current scientific evidence indicates regarding

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ARTICLE HIGHLIGHTS

- Normal physiologic levels of testosterone are beneficial to the male cardiovascular (CV) system, and testosterone deficiency is associated with an unfavorable metabolic profile and increased CV disease events.
- The Food and Drug Administration, the American Association of Clinical Endocrinologists/American College of Endocrinology, and an international consensus panel all state that testosterone therapy is safe and reasonable in patients with symptomatic testosterone deficiency.
- Testosterone treatment should be considered for symptomatic men with clinically confirmed hypogonadism; there is no compelling evidence that testosterone therapy either increases or decreases CV disease risk, and testosterone therapy for men with hypogonadism is effective, rational, and evidence based.
- A major research initiative is needed to explore the possible cardioprotective effects of testosterone therapy.

the relationship between both endogenous testosterone levels and testosterone therapy and CV health and to summarize current recommendations and directions for future research.

A literature review was conducted via search using PubMed and specific journal databases, including the *New England Journal of Medicine* and the *Journal of the American College of Cardiology*. Key search terms included *testosterone and cardiovascular health*, *coronary artery disease*, *heart failure*, *androgen deprivation therapy*, *intima-media thickness*, and *adrenal androgens*. Initial study selection was limited to publications in the past 10 years (January 1, 2007, through December 31, 2016); however, key publications outside of this time frame were selected if they provided important quantitative data or historical perspectives for the review of this topic. The search was further supplemented by reviewing references in selected articles.

ANDROGENS IN THE MALE

Under the control of the pituitary hormones luteinizing hormone and follicle-stimulating hormone (FSH), the Leydig cells of the testes produce testosterone. In males, 95% of circulating testosterone is derived from testicular production (3-10 mg/d).[14] Testosterone causes virilization of the external male genitalia during embryonic development, promotes somatic growth and secondary sexual characteristic development (adrenarche) in puberty, and is necessary for spermatogenesis, stimulation of libido, normal sexual function, and maintenance of muscle and bone mass in adults.[14] Androgen deficiency may be caused by gonadotropin deficiency or primary testis dysfunction. The effects of testosterone include bone formation, increased muscle mass, spermatogenesis, prostate growth, acne, facial/body hair development, and scalp hair loss.[14] Excess testosterone and testosterone therapy have been associated with worsening of sleep apnea, gynecomastia, polycythemia, and prostate-specific antigen level elevation.[15]

UNDERSTANDING THE CONTROVERSY

Several studies have reported an inverse association between endogenous testosterone levels and adverse CVD outcomes, independent of traditional risk factors.[16] These findings suggested a possible cardioprotective effect of testosterone, which may, in part, have led to significant increases in prescriptions for testosterone in the following years.[17,18] One study collected data for testosterone product sales from 2000 through 2011 for 41 countries, including the United States, Canada, the United Kingdom, and Australia, and found that total testosterone sales increased 12-fold globally, rising from $150 million in 2000 to $1.8 billion in 2011.[18] The most dramatic increases in testosterone use were seen in Canada and the United States.

Following the trend of increased testosterone prescriptions, trials emerged that found an increased CVD risk with testosterone therapy. The FDA began investigating the potential increased risk of CVD events with testosterone therapy in 2010 owing to premature cessation of the Testosterone in Older Men With Mobility Limitations (TOM) trial,[19] which was stopped before enrollment was completed due to the higher incidence of CVD events in the testosterone treatment group.[20] The TOM trial was critiqued for the lack of a consistent pattern of CVD events, which ranged from edema to MI and death, as well as the small sample size and small number of CVD events (CVD events occurring in 23 patients in the

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treatment group vs 5 patients in the placebo group), possibly indicating that the differences may have been due to chance alone.[21] After an intense literature review, the FDA concluded that there was insufficient evidence of an increased risk of CVD events due to testosterone therapy at that time.[20]

Trials by Vigen et al[22] in 2013 and Finkle et al[23] in 2014 received major media attention following reports of increased mortality, MI, and stroke in men receiving testosterone therapy. Both of these studies were later found to be critically flawed. One study had 2 official corrections, including a later report of a 50% lower rate of CVD events in men receiving testosterone therapy, and the other had no control group.[6] Following the increased controversy that came with these trials, in March 2015, the FDA published a drug safety communication regarding the use of testosterone-containing products, warning about a potential increase of CVD events.[24] The FDA released a statement advising increased caution when prescribing testosterone therapy, which some professional societies, including the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), as well as an international expert consensus panel felt was lacking scientific evidence.[6,13]

At this time, the FDA also mandated new labeling of testosterone-containing products to highlight the potential increased CVD risk and limited the approved indications for testosterone therapy to hypogonadism of known etiologies, making the treatment of hypogonadism due to aging and idiopathic hypogonadism off label.[20] It has been argued that there has been no scientific justification for the FDA's recommendation that testosterone therapy be reserved for conditions of testosterone deficiency of specific, known etiologies.[6] During the past 20 years, several new causes of testosterone deficiency have been identified, and more will likely be found in the future.[6] Considering that approximately 80% of individuals with hypertension have no known underlying etiology, an analogy can be made that to reserve testosterone therapy for only those with a clearly defined etiology of testosterone deficiency would be akin to reserving hypertension therapy for the 20% of individuals with hypertension who have a known cause.[6] It is agreed by the 2015 international expert consensus conference regarding testosterone deficiency and the 2015 AACE/ACE position statement on the association of testosterone and CVD risk that testosterone treatment need not be reserved only for known etiologies of testosterone deficiency.[6,13] Specifically, the AACE/ACE recommend that symptomatic men who have low total or free testosterone levels on at least 2 samples collected before 10 AM should be considered for testosterone replacement therapy.[13]

The FDA defines hypogonadism as testosterone levels of 300 ng/dL or less (to convert to nmol/L, multiply by 0.0347), with no mention of symptoms in the definition, and the Endocrine Society defines hypogonadism as the presence of both low testosterone levels and hypogonadal symptoms.[20] Many professional societies have recommended that the FDA change its definition of hypogonadism to include symptoms such as decreased libido, erectile dysfunction, depression, and fatigue.[20] The AACE/ACE position statement on the association of testosterone and CVD risk concludes that there is no compelling evidence that testosterone therapy either increases or decreases CVD risk.[13] It is thought that the FDA's decision to advise increased caution with testosterone use was driven by a combination of factors, including the dramatic increase in the number of testosterone prescriptions, direct-to-patient marketing by drug companies, and the absence of high-quality data demonstrating the safety and efficacy of testosterone therapy in the treatment of hypogonadism.[20]

On October 1, 2015, an international expert consensus conference regarding testosterone deficiency and its treatment was held in an attempt to clarify the accepted scientific evidence regarding the relationship between testosterone and CV health. This conference produced 9 conclusive statements, termed *resolutions*, which received unanimous approval.[6] The unanimous approval of these resolutions does not imply that there is no further controversy regarding these issues. The panel concluded that testosterone deficiency is a well-established medical condition that is a global public health concern. Data from the Massachusetts Male Aging Study predicted an incidence of 481,000 new cases of androgen deficiency per year in men aged 40 to 69 years

TABLE. Key studies examining the effects of testosterone therapy on CV health

Reference, year	Population	Sample size (No.)	Major findings	Suggests benefit (+) or risk (−) of testosterone therapy
Iellamo et al,[28] 2010	Elderly women with CHF	36	Improved functional capacity, insulin resistance, and muscle strength	+
Caminiti et al,[29] 2009	Elderly men with CHF and low serum testosterone levels	70	Improved exercise capacity, muscle strength, glucose metabolism, and BRS	+
Mirdamadi et al,[30] 2014	Men with CHF	50	Testosterone treatment group had a significant increase in 6MWT distance	+
Toma et al,[31] 2012	Patients with CHF receiving testosterone	Meta-analysis	Testosterone supplementation in CHF associated with improvement in 6MWT Testosterone treatment significantly improved fasting glucose, fasting insulin, and insulin resistance No safety concerns in any of the trials, but data limited due to small samples and short follow-up	+
Traish et al,[32] 2017	Elderly men with low serum testosterone levels	656	Testosterone therapy was associated with an estimated mortality reduction of 66%-92% Less stroke and MI in the testosterone treatment group	+
Budoff et al,[16] 2017	Elderly men with low serum testosterone levels	138	Testosterone therapy was associated with a significant increase in noncalcified and total coronary plaque	−
Wallis et al,[33] 2016	Elderly men receiving testosterone therapy	38,340	Patients treated with testosterone had lower mortality rates and fewer CV events than controls	No risk
LeBrasseur et al,[19] 2009	Elderly men with low serum testosterone levels	252	Trial stopped before enrollment completed due to a higher incidence of CV events in the testosterone treatment group	−
Cheetham et al,[34] 2017	Men aged ≥40 y with low serum testosterone levels	44,335	Fewer CV events in the testosterone treatment group; HR, 0.67 (95% CI, 0.62-0.73) Higher rate of CV events in patients with higher baseline testosterone levels (>400 ng/dL); HR, 1.64 (95% CI, 1.06-2.54)	+ in patients with low serum testosterone levels, caution in patients with normal serum testosterone levels
Maggi et al,[35] 2016	Men with low serum testosterone levels	999	No evidence of increased mortality or CV events in men receiving testosterone therapy compared with untreated men Concluded that age and prior CV history, not testosterone therapy, were predictors of CV events	+

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TABLE. Continued

Reference, year	Population	Sample size (No.)	Major findings	Suggests benefit (+) or risk (−) of testosterone therapy
Alexander et al,[36] 2017	Men aged ≥18 y receiving testosterone therapy	Meta-analysis reviewing 39 RCTs and 10 observational studies	Compared with placebo use, exogenous testosterone treatment did not significantly increase MI (OR, 0.87; 95% CI, 0.39-1.93; 16 RCTs), stroke (OR, 2.17; 95% CI, 0.63-7.54; 9 RCTs), or mortality (OR, 0.55-1.41; 20 RCTs) Evidence was rated low quality due to high risk of bias, imprecision, and inconsistency No definitive conclusion on CV effects of testosterone therapy	NA
Sharma et al,[37] 2016	Patients with low serum testosterone levels	71,407	No significant difference in rates of DVT/PE in patients receiving testosterone	No risk
Haider et al,[38] 2016	Men with low serum testosterone levels and a history of CVD	77	Testosterone therapy seems to achieve sustained improvements in cardiometabolic risk factors, including lipid pattern, glycemic control, BMI reduction, weight loss Blood pressure, heart rate, and pulse pressure all improved	+
Webb et al,[39] 2008	Men aged 40-75 y with angiographically proven CAD (>70% in ≥1 major coronaries or major branches)	23	Oral testosterone therapy in men with CAD and low testosterone levels modestly increased myocardial perfusion in myocardium supplied by unobstructed coronary arteries, whereas perfusion areas with significant obstruction were not affected	+
Mathur et al,[40] 2009	Men with stable, chronic angina	13	Testosterone treatment group had increased mean ± SD time to ischemia (117.8±21 seconds; 95% CI, 72-164 seconds)	+
Webb et al,[41] 1999	Men with CAD and low testosterone levels	14	Testosterone treatment group had increased time to 1-mm ST depression compared with the placebo group by 66 seconds (range, 15-117 seconds) (P=.016)	+

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TABLE. Continued

Reference, year	Population	Sample size (No.)	Major findings	Suggests benefit (+) or risk (−) of testosterone therapy
Aversa et al,[42] 2010	Middle-aged men with low testosterone levels	50	Testosterone treatment was associated with a marked improvement in insulin resistance ($P<.001$), carotid IMT ($P<.0001$), and hs-CRP ($P<.001$)	+
Francomano et al,[43] 2014	Severely obese men (mean BMI, 42)	24	Testosterone treatment group had improvements in EF, diastolic function, carotid IMT, and endothelial function ($P<.01$ vs controls), in addition to improvements in metabolic and inflammatory parameters 24 wk after testosterone withdrawal, all cardiac and hormonal parameters returned to baseline	+
Rai and Ramasamy,[44] 2016	Men with low or low-normal testosterone levels who received testosterone therapy	306	No difference in the progression of subclinical atherosclerosis, as measured by carotid IMT or CAC, between groups	No benefit

6MWT = 6-Minute Walk Test; BMI = body mass index; BRS = baroreflex sensitivity; CAC = coronary artery calcium; CAD = coronary artery disease; CHF = chronic heart failure; CV = cardiovascular; CVD = cardiovascular disease; DVT = deep vein thrombosis; EF = ejection fraction; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; IMT = intima-media thickness; MI = myocardial infarction; NA = not available; OR = odds ratio; PE = pulmonary embolism; RCT = randomized controlled trial.

in the United States.[25] One US study estimated that over a 20-year period, testosterone deficiency may have been directly responsible for approximately $190 billion to $525 billion in US health care expenditures.[26]

Another resolution of the international expert consensus panel states that testosterone therapy for men with testosterone deficiency is effective, rational, and evidence based.[6] The panel also concluded that the evidence does not support increased risks of CVD events with testosterone therapy, which is in accordance with the AACE/ACE position statement on the association of testosterone and CV health.[6,13] They support this final statement, citing the inverse relationship of testosterone levels with atherosclerosis, diabetes, obesity, CAD, and death as well as several randomized controlled trials in men with known CVD reporting greater benefits with testosterone therapy compared with placebo.[6] The panel concluded that there is a need for a major research initiative to explore the possible cardioprotective benefits of testosterone therapy, implying that there is sufficient evidence regarding the safety of testosterone therapy in hypogonadal males and that the direction of future research should be set toward defining suitable therapeutic options. We believe that ongoing research efforts should focus on epidemiology, disease risk associations, pathophysiology, molecular pharmacotherapeutics, and health-related outcomes of the diagnosis and treatment of testosterone deficiency.[27] See the Table for key findings of studies that analyzed the relationship between testosterone therapy and CV health.

ENDOGENOUS TESTOSTERONE AND CV HEALTH

Testosterone reaches maximum levels in men at approximately age 30 years, after which levels steadily decline at a rate of 1% to 2% annually.[17] Endogenous levels of serum testosterone fluctuate by a circadian pattern, as well as in response to stress. Testosterone levels drop abruptly with acute illnesses, such as MI, sepsis, or trauma, and low testosterone levels are associated with several chronic conditions, including diabetes, renal failure, malignancy, hypertension, and dyslipidemia.[2,17,18,45] This fluctuation of testosterone levels according to various disease states complicates the assessment of a

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potential cause-and-effect relationship between testosterone levels and CV health due to the large number of associated variables. These variables are confounding considering that CVD occurs most commonly in elderly men and that elderly men typically have lower levels of serum testosterone as well as increased chronic disease burden. Although there is evidence of testosterone deficiency being associated with increased mortality in multiple cohort studies, it remains unclear whether this is a causal relationship or due to low testosterone level being a biomarker of poor overall health.[2] Therefore, a high testosterone level in elderly men may be a sign of good general health and thereby is associated with reduced risk of CVD events.[45]

Much of the current literature suggests that testosterone deficiency is associated with unfavorable health effects. Testosterone deficiency is associated with loss of bone and lean body mass, increased adiposity, low energy, and impaired physical and sexual function.[12] Testosterone levels correlate positively with high-density lipoprotein and negatively with low-density lipoprotein and the inflammatory state.[1] Epidemiologic studies have found that low serum testosterone levels are associated with more atherosclerosis, CAD, and CVD events.[45,46] Low serum testosterone level is also strongly associated with an adverse metabolic risk profile, including insulin resistance, diabetes mellitus, and high body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared).[5,12,17,45] Ohlsson et al[45] report that high serum testosterone level predicted a 5-year reduced risk of CVD events in elderly men. Akishita et al[47] studied a population of 171 men, finding that those in the lowest tertile of serum testosterone levels were more likely to develop CVD events than those in the highest tertile ($P<.01$) after adjustment for coronary risk factors. A study of 3014 men found that free testosterone was independently and positively associated with ankle-brachial index measurements ($P<.001$), suggesting an association between low serum testosterone level and peripheral arterial disease.[48] A study of 69 men younger than 45 years with premature CAD also found that low testosterone levels were associated with a 3.3 fold higher risk of developing premature CAD compared to those with free testosterone level above the cut-off level of 17.3 pg/ml.[7] These findings suggest a possible cardioprotective effect of normal physiologic levels of testosterone. However, no causal relationship has been proved, and it remains uncertain whether CVD or an overall poor state of health causes testosterone deficiency, or vice versa. Overall, the evidence indicates that a normal physiologic level of testosterone is beneficial, and deficiency is associated with many unfavorable findings, including multiple CVD risk factors, as outlined in Figure 1.

SYMPTOMATIC HYPOGONADISM

Current recommendations from the AACE/ACE state that testosterone therapy should be considered in patients with symptomatic hypogonadism.[13] Cheetham et al[34] found that CVD events occurred at rates of 23.9 per 1000 person-years in patients with symptomatic hypogonadism who never received testosterone therapy vs 16.9 per 1000 person-years in those who had received treatment, with an adjusted hazard ratio (HR) for CVD events of 0.67 (95% CI, 0.62-0.73) with testosterone therapy. These findings suggest that testosterone therapy in hypogonadal patients may have a cardioprotective effect. This study also found that patients with baseline testosterone levels greater than 400 ng/dL had a higher adjusted HR for CVD events (HR, 1.64; 95% CI, 1.06-2.54), which adds to the pool of evidence suggesting caution when using testosterone therapy in men with normal testosterone levels, such as the example of increased CVD events in males who abuse anabolic steroids. This is in accordance with current recommendations from the AACE/ACE.

The RHYME (Registry of Hypogonadism in Men) trial[35] found no evidence of increased mortality or CVD events in hypogonadal men receiving testosterone therapy compared with those untreated. The lack of an association persisted between older and younger patients, primary and secondary hypogonadism, and injectable and topical modes of testosterone therapy. The study investigators concluded that age and a CVD history, not testosterone therapy, were predictors of CVD events. An observational study consisting of 77 hypogonadal men with a history of CVD being treated with testosterone therapy for up to 8 years found an improvement in metabolic parameters without a single adverse CVD event during the full observation time.[38] The authors reported that testosterone therapy seemed to achieve a sustained improvement in

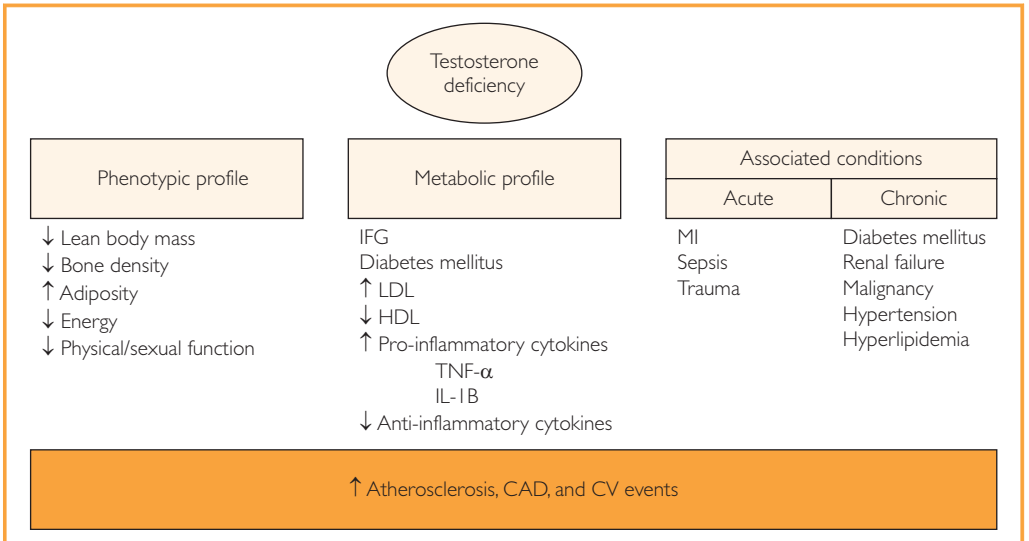

FIGURE 1. Testosterone deficiency and cardiovascular (CV) disease. Testosterone deficiency is associated with multiple acute and chronic conditions. Although testosterone levels drop in the acute setting after myocardial infarction (MI), sepsis, and trauma, it is unknown whether testosterone deficiency has a causal role in chronic diseases or whether chronic disease states cause testosterone deficiency. Testosterone deficiency is also associated with phenotypic and metabolic profiles that are known to be associated with atherosclerosis and CV disease. CAD = coronary artery disease; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IL = interleukin; LDL = low-density lipoprotein; TNF = tumor necrosis factor.

cardiometabolic risk factors, including lipid pattern, glycemic control, BMI, and weight loss. These authors argue that testosterone therapy may be effective for secondary prevention of CVD events in hypogonadal men with CVD.

Although the improvement of cardiometabolic parameters with testosterone supplementation has been reported in multiple studies, there are trials suggesting that these benefits are sustained only with continued testosterone therapy. The study by Francomano et al,[43] which is discussed in greater detail in a later section, found that testosterone therapy was associated with improvements in ejection fraction (EF), diastolic function, and carotid intima-media thickness (IMT) in addition to improvements in metabolic and inflammatory parameters. However, 24 weeks after testosterone withdrawal, all cardiac and hormonal parameters returned to baseline. Further studies are needed to determine the longevity of potential CV benefits of testosterone therapy.

A recent observational, prospective, cumulative registry trial by Traish et al[32] followed 656 men with total testosterone levels of 12.1 nmol/L or less and symptoms of hypogonadism. A total of 360 patients received testosterone undecanoate 1000 mg/12 weeks for up to 10 years, and 296 patients who opted against testosterone therapy (primarily for financial reasons) served as controls. In the testosterone treatment group, there were 2 deaths, neither of which were related to CVD events, and the control group had 21 deaths, 19 of which were related to CVD events. There were also 30 nonfatal strokes and 26 nonfatal MIs in the control group and none in the treatment group. The estimated reduction in mortality for the treatment group was 66% to 92%. One important limitation of this study is that patients with Klinefelter syndrome, primary hypogonadism, or inflammatory disease were considerably younger and exclusively in the treatment group, resulting in an average age difference of 57.4 vs 64.8 years in the treatment vs control groups. These findings are consistent with the most recent 2010 Endocrine Society guidelines and FDA recommendations for testosterone therapy, that it should be used to treat patients with symptomatic hypogonadism, and the scientific

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evidence does not indicate an increased CVD risk in this patient population.

TESTOSTERONE AND CAD

Despite regional variations in the prevalence of CAD, men are consistently at an approximately 3-fold increased risk compared with women to develop CAD, and men often develop the disease a decade earlier.[1] Although testosterone deficiency is not considered a traditional risk factor for CAD, it is widely accepted that men experience a gradual decline in testosterone levels with increasing age and that male sex has long been considered a strong risk factor for CAD.[17] Many studies have been conducted to investigate the relationship between testosterone and CAD, and although there is a growing body of evidence suggesting that testosterone deficiency has a much stronger association with CAD than controls with normal coronary arteries, the evidence has been conflicting.

Explanations for the inconsistency of earlier reports regarding the association between testosterone deficiency and CAD include variability in the study design, in the assays applied, in the measures of testosterone quoted, and in the definitions of hypogonadism and cardiovascular disease used.[1] Multiple studies reveal an inverse association between testosterone levels and coronary artery calcium (CAC) scores.[49,50] There have also been studies suggesting that testosterone levels serve as an independent predictor of CAD severity when assessed via Gensini score.[8] Studies involving men younger than 45 years with premature CAD have also found low testosterone levels in patients with CAD compared with controls.[7] Although the correlations have been demonstrated with reproducible results, it is not possible to determine a cause-and-effect relationship. Testosterone levels may directly cause (or prevent) CAD and CVD events, or testosterone levels may simply be a marker of overall quality of health and have no direct effect on CAD and CVD events at all.

Malkin et al[12] reported that in a population of 930 men with known CAD, those with testosterone deficiency had excess mortality compared with those with normal testosterone levels (21% vs 12%; P=.002). Multivariate analyses indicated that low serum testosterone level was an independent parameter that influenced time to mortality, alongside left ventricular dysfunction, aspirin therapy, and β-blocker therapy. If further studies validate low serum testosterone level as an independent predictor of mortality in patients with CAD, it may be used as a valuable prognostic indicator in this patient population, or perhaps as therapy to reduce mortality. The authors of this study conclude that testosterone deficiency has a significant negative effect on survival in patients with CAD.[12]

Budoff et al[16] studied 138 testosterone-deficient men 65 years and older to assess the effects of testosterone therapy on coronary artery plaque volume, assessed by coronary computed tomographic angiography (CCTA). Of 138 men who completed the study, 73 received testosterone therapy and 65 received placebo. At baseline, the treatment group had lower median noncalcified plaque volume vs the placebo group (204 mm^3 vs 317 mm^3) and lower median total plaque volume (272 mm^3 vs 499 mm^3). At 12 months, it was found that the testosterone treatment group had a significantly greater increase in median noncalcified plaque volume (treatment group: from 204 mm^3 to 232 mm^3 vs placebo group: from 317 mm^3 to 325 mm^3; P=.003) and median total plaque volumes (treatment group: from 272 mm^3 to 318 mm^3 vs placebo group: from 499 mm^3 to 541 mm^3). Testosterone therapy in this study of hypogonadal men with CAD was associated with significant increases in coronary plaque volume. There was no significant change in CAC score in the testosterone treatment group. In this study, testosterone treatment was associated with a significant increase in the fibrous and total plaque burden. No participants in this trial experienced a major adverse CVD event, but the major limitation was that the study was not large enough or long enough to draw conclusions about the risk of testosterone treatment on major adverse CVD events. Note that the participants in this study had relatively high rates of obesity and concomitant illnesses, such as hypertension, hyperlipidemia, and diabetes, as well as high 10-year CV risk scores (24% in the treatment group and 27% in the placebo group) according to the American College of Cardiology/American Heart Association risk calculator, and reasons for plaque progression other than testosterone treatment alone should be

considered in the interpretation of these results. Whereas Malkin et al[12] reported low serum testosterone level to be an independent parameter that influenced time to mortality in patients with CAD, suggesting a possible therapeutic role of testosterone therapy, the study by Budoff et al[16] suggests caution when using testosterone therapy in patients with known CAD due to a possible worsening of overall plaque burden.

Intracoronary testosterone infusions induce coronary vasodilation and increase coronary blood flow, a finding that has made testosterone supplementation a potential therapeutic option for patients with angina and CAD.[12,39] A study involving 13 patients—7 receiving testosterone treatment and 6 receiving placebo—found an increased time to ischemia in patients with chronic angina and proven ST depression greater than 1 mm within 12 minutes on the Bruce protocol.[40] The mean ± SD increase in time to ST depression was 117.8±21 seconds (95% CI, 72-164 seconds). The authors cited in vitro studies that found inhibition of testosterone on L-type calcium channels, which is the same site of action as nifedipine, which may be the mechanism of the anti-ischemic effect.[40] Note that testosterone has a known dose-dependent stimulatory effect on erythropoiesis.[44] The investigators of this trial reported that the testosterone treatment group also had an increase in hemoglobin levels, which may have contributed to the increased time to ischemia if the patients in the treatment group were significantly anemic. This was not the first study to report a beneficial effect of testosterone therapy on exercise-induced myocardial ischemia. Another small (n=14), randomized, double-blind, crossover study found that testosterone therapy in hypogonadal men with known CAD had increased time to 1-mm ST depression compared with placebo by 66 seconds (P=.016).[41]

It is clear that testosterone deficiency is associated with increased adverse CVD events, including mortality.[12,48,51,52] Although there are reports that suggest possible acceleration of coronary plaque progression with testosterone therapy,[16] these findings must be reproduced before conclusions are drawn. A recent systematic review and meta-analysis by Alexander et al[36] reviewed 39 randomized controlled trials and 10 observational studies and found that exogenous testosterone treatment, compared with placebo use, did not result in any significant increase in MI, stroke, or mortality. However, the evidence received a low quality rating due to the high risk of bias, imprecision, and inconsistency among trials. Therefore, no definitive conclusion on CV effects of testosterone could be reached. The ongoing Cardiovascular Trial of The Testosterone Trials will test the hypothesis that testosterone therapy inhibits coronary plaque progression as assessed by serial CCTA.

TESTOSTERONE AND IMT

Multiple studies have examined the association between endogenous testosterone levels and IMT of various major blood vessels as a marker of atherosclerosis. Many of these studies have found an association of increased IMT with low serum testosterone levels.[3,9-11] It is interesting that the association between testosterone deficiency and increased IMT was reproduced in very phenotypically different populations, including aging men, obese adolescent females, and patients with classic congenital adrenal hyperplasia. Many of these studies also noted a high prevalence of metabolic syndrome or insulin resistance in their patient population, which makes it difficult to assess whether the apparent atherosclerosis may be caused by the low serum testosterone levels, metabolic disturbances, or some unrelated process.[3,9,11]

One study of 1482 men aged 25 to 84 years found an inverse association between total testosterone levels and carotid IMT, but this finding was not independent of BMI, suggesting that the relationship between total testosterone level and IMT is at least partially mediated by body fat or body fat distribution.[4] Another study treated patients with metabolic syndrome and testosterone deficiency with parenteral testosterone undecanoate and found a marked improvement in insulin resistance, carotid IMT, and high-sensitivity C-reactive protein levels (all P<.001).[42] Another study found a similar beneficial effect on carotid IMT with testosterone therapy, which was reversed after withdrawal of therapy. Twenty-four hypogonadal, severely obese (mean BMI, 42) men were randomized to receive a calorie-restricted diet alone vs a diet with testosterone therapy. At 54 weeks, the

diet plus testosterone therapy group had improvements in EF, diastolic function, carotid IMT, and endothelial function ($P<.01$ vs controls), in addition to improvements in metabolic and inflammatory parameters.[43] After withdrawal of testosterone therapy, all cardiac and hormonal parameters returned to baseline, with the loss of CV improvements.[43]

Rai and Ramasamy[44] describe a trial involving 306 men with low or low-normal testosterone levels who received testosterone therapy and found no difference in the progression of subclinical atherosclerosis with the placebo group, as measured by carotid IMT or CAC. It is possible that the inclusion of patients with low-normal testosterone levels in this study may account for the lack of a difference in markers of atherosclerosis. Although most studies report the association between low serum testosterone level and increased atherosclerosis, no threshold has yet been established. One study of 876 men aged 45 to 75 years following locally weighted regression found that a testosterone threshold of 440 ng/dL was associated with increased Framingham 10-year CVD risk in middle-aged and elderly men.[51] Further studies are required for validation of these findings.

TESTOSTERONE AND HEART FAILURE

The role of testosterone in the pathogenesis and progression of heart failure (HF) is a topic of increasing interest. Heart failure is a unique metabolic syndrome characterized by numerous endocrine, metabolic, and inflammatory parameters, and approximately 25% of men with chronic HF have biochemical evidence of testosterone deficiency, which has been associated with progression of HF.[52] As mentioned previously, testosterone levels are often reduced in states of acute and chronic illness. In addition, hepatic congestion in patients with HF can lead to an increase in sex hormone binding globulin (SHBG) levels, with a subsequent further decrease in free testosterone levels.[46] It has also been found that testosterone levels are decreased in proportion to HF severity.[53]

Myocardial cachexia, a syndrome with a poor prognosis, is characterized by particularly low testosterone levels.[52] Cachexia, from the Greek "kakos" (bad) and "hexis" (condition), is a dreaded yet frequent accompaniment of advanced HF that signifies a greater burden of morbidity and mortality.[54] Obesity confers a favorable prognosis in HF, referred to as the obesity paradox, in which patients with HF tend to live longer if designated as obese.[54-56] This obesity paradox is a well-established phenomenon and occurs regardless of age, ethnicity, or severity of CVD.[57] Cardiac cachexia has a mortality rate in patients with HF as high as 50% at 18 months compared with 17% in noncachectic patients.[58] A proposed mechanism for myocardial cachexia involves the concept of bioenergetic starvation, in which there is a vicious cycle of insulin resistance and metabolic failure, which results in a global imbalance between catabolic and anabolic signals in the myocardium as well as peripheral tissues, which leads to tissue wasting and, ultimately, cachexia.[59] The association of testosterone deficiency with myocardial cachexia, progression of HF, and decreased insulin sensitivity, which can cause muscle fatigue via impaired glucose uptake by muscle cells, has led to the rationale that correcting testosterone deficiency in HF may be a therapeutic option.

Multiple investigators have explored the effects of testosterone supplementation in patients with HF. Intravenous testosterone administration can increase cardiac output and reduce peripheral vascular resistance, and chronic therapy can reduce circulating inflammatory mediators and potentially reduce left ventricular fibrosis.[46] A meta-analysis by Toma et al[31] found that testosterone supplementation in patients with HF was associated with improved exercise function using the 6-Minute Walk Test, as well as metabolic parameters such as fasting glucose, fasting insulin, and insulin resistance. No safety concerns were reported in any of the trials; however, data were limited due to small samples and short follow-up.

Caminiti et al[29] studied the effects of 12-week testosterone administration on exercise capacity, ventilator efficiency, muscle strength, insulin resistance, and baroreflex sensitivity in elderly patients with chronic HF. Seventy patients were enrolled, with a median age of 70 years and a mean ± SD EF of 31.8%±7%, New York Heart Association class II or III HF, and clinically stable with no hospital admissions for HF in the previous 3 months. These patients were randomly assigned to receive an intramuscular injection of either

testosterone undecanoate (1000 mg) or saline every 6 weeks. The authors concluded that long-acting testosterone therapy improved exercise capacity, muscle strength, glucose metabolism, and baroreflex sensitivity.

Critics of the study by Caminiti et al[29] argued that the improved physical performance in patients receiving testosterone therapy may have been secondary to the substantial mood-elevating effects of testosterone therapy; at one time, testosterone was patented as an antidepressant agent.[60] However, Malkin et al[61] also reported an improvement in functional capacity in patients with HF treated with supplemental testosterone at physiologic doses and was not accompanied by any change in mood scores. Findings of increased exercise capacity in patients with HF receiving testosterone therapy were also reported by Pugh et al.[62] Beneficial findings were also seen in a study of women with advanced HF (mean ± SD EF, 32.9%± 6%) by Iellamo et al,[28] who found an improvement in functional capacity, insulin resistance, and muscle strength in women with HF receiving testosterone therapy compared with placebo. Fifty males with HF receiving testosterone therapy also had a significant increase in 6-Minute Walk distance in a study by Mirdamadi et al.[30]

No studies were found during this literature review that reported an improvement in left ventricular EF after testosterone therapy in patients with HF. Multiple authors have reported that if testosterone does, indeed, have a positive clinical effect on patients with HF, defined as reduced CVD events or improved functional/exercise capacity, it is likely due to peripheral mechanisms.[28,29,53] The symptoms of HF are dictated by many more factors than the degree of myocardial dysfunction alone. Therefore, other mechanisms of skeletal muscle dysfunction have been suggested, such as insulin resistance leading to an inability of glucose transport into skeletal muscle as a cause of weakness.[52] The associations between testosterone deficiency and insulin resistance, among other metabolic derangements, therefore, again, make testosterone therapy an attractive therapeutic option that requires further study.

ANDROGEN DEPRIVATION THERAPY

Multiple studies have reported that low testosterone levels correlate with poor CV health and increased CVD events. In a scenario in which testosterone levels are intentionally reduced, such as with the use of ADT for prostate cancer, an increase in CVD events would support the hypothesis that testosterone deficiency causes increased CVD events, particularly if these findings occur in subjects lacking traditional CVD risk factors. Many studies have been conducted to investigate whether ADT has effects on CV health.

Androgen deprivation therapy has been the mainstay of treatment for advanced prostate cancer since its discovery in 1941, and treatments include gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, orchiectomy, estrogens, and antiandrogens.[63] Although ADT has been found to be effective for reducing rates of recurrence as well as palliation, ADT is also associated with reduced quality of life, sexual dysfunction, fatigue, anemia, and loss of bone density.[64] Multiple studies describe increased CVD events with GnRH agonist therapy compared with other forms of ADT, such as GnRH antagonist therapy or bilateral orchiectomy.[63,65,66] There is evidence of some mechanisms that may be responsible for these findings, as outlined in Figure 2. First, GnRH receptors have been found on T lymphocytes, which are known to be a part of atheromatous plaques, and the activation of which can lead to plaque instability.[63] There is also accumulating experimental and clinical data indicating that FSH has a role in inflammation, atherosclerosis, insulin resistance, formation of reactive oxygen species, and adipocyte rearrangement.[67] In animal studies, mice receiving GnRH antagonists had significantly lower FSH levels compared with mice receiving GnRH agonists or orchiectomy. Mice receiving GnRH agonists or orchiectomy (higher FSH levels) had more than double the atherosclerotic plaque development of mice receiving GnRH antagonists (lower FSH levels).[67] Several studies have found that ADT, especially involving GnRH agonists, is associated with increased CVD risks, which consequently led the US FDA to issue a safety warning in 2010 requiring labeling on GnRH agonists about an increased risk of CVD.[65] Despite this, the relationship between ADT and CVD events remains controversial, and a recent meta-analysis of randomized trials did not find an association

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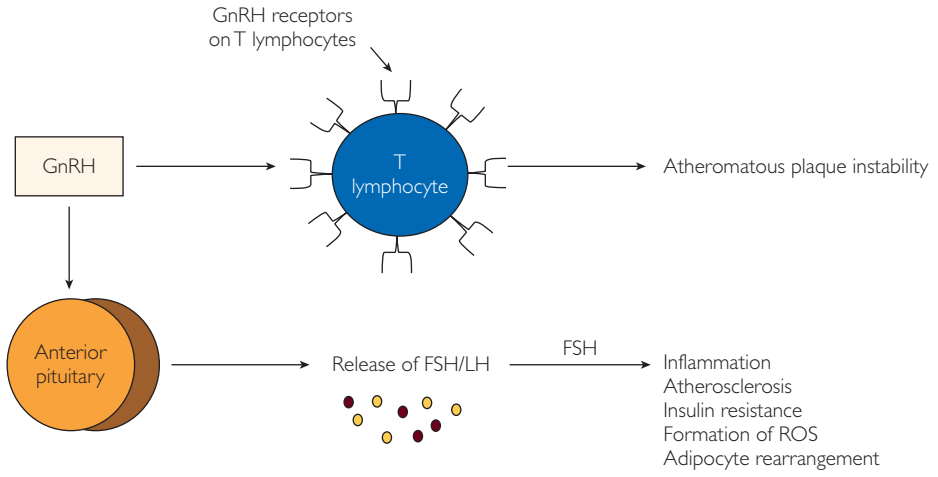

FIGURE 2. Proposed mechanisms of increased cardiovascular events with gonadotropin-releasing hormone (GnRH) agonist therapies. The GnRH receptors have been found on T lymphocytes, which are known to be a part of atheromatous plaques, the activation of which can lead to plaque instability. There is also accumulating experimental and clinical data indicating that follicle-stimulating hormone (FSH) has a role in inflammation, atherosclerosis, insulin resistance, formation of reactive oxygen species (ROS), and adipocyte rearrangement. LH = luteinizing hormone.

between ADT and CVD mortality, although multiple authors have argued that clinical trials usually enroll younger and healthier patients, who might be considered at reduced risk for CVD morbidity and mortality.[63,65]

Bosco et al[63] found that ADT with GnRH agonists had a 38% increased risk of any type of nonfatal CVD compared with patients with prostate cancer not receiving ADT. The associations were higher for MI (57%) and stroke (51%) as well. Another study analyzed data from 140,474 patients in the United States matched by a propensity scoring system to analyze the association of ADT with CAD, acute MI, and sudden cardiac death (SCD).[65] Acute MI, CAD, and SCD were all higher in the GnRH agonist group than in the non-ADT or orchiectomy group. Particularly at 10-year follow-up, the rates of CAD, acute MI, and SCD were 27%, 16%, and 17%, respectively, vs 25%, 15%, and 14% in the ADT-naive group.[65] These results are similar to those reported by Keating et al,[66] who studied 73,196 patients and found that GnRH agonist therapy was associated with an increased incidence of diabetes, CAD, MI, and SCD. Orchiectomy was not associated with an increased risk of CAD, MI, or SCD in either study.

However, there are also large trials that did not find a significant association between ADT and CVD events. One such study, analyzing 19,079 patients with prostate cancer who received ADT matched with patients with prostate cancer who had never received ADT found a positive association with diabetes and fragility fracture in the ADT treatment group but not with acute MI or SCD.[64] In this study, 5.5% of non-ADT patients (n=1085) vs 4.8% of ADT-treated patients (n=949) experienced MI. Rates of SCD were also lower in the ADT treatment group (2%; n=399) vs the non-ADT treatment group (2.2%; n=436). After risk adjustment, the authors reported an increased risk of diabetes but not MI or SCD and also found a lower likelihood of stroke. The authors also report that the large number of events and more extensive adjustment for comorbidities, as well as a definition for MI with a lower false-positive rate (Ontario MI database algorithm, with sensitivity of 95% and a false-positive rate <5%) are strengths not found in some of the studies reporting increased CVD events with ADT treatment, including the study by Keating et al.[66] These findings are in accordance with the European Association of

Urology's 2012 prostate cancer guidelines,[68] which state that the evidence regarding ADT and CVD mortality risk is not consistent.[63]

It would be ideal to study the effects of ADT in patients lacking risk factors for CVD in an attempt to establish a causal connection between testosterone deficiency and CVD. Considering that prostate cancer occurs in elderly men, it is difficult to find a cohort of men undergoing ADT who lack traditional CVD risk factors to study. Wu and von Eckardstein[69] described studies that examined the effects of castration on CV health. They reviewed a study of 297 castrated inmates in a Kansas institution for the mentally retarded between 1895 and 1950, as well as a study of 50 castrated singers born between 1851 and 1858 compared with 50 noncastrated singers, finding no significant increase in mortality due to CVD.[69] However, these are very old studies and may have had different results if analyzed by modern research methods and statistical analysis. They do, however, provide important information about cohorts that no longer exist in the developed world, and their findings should not be discarded completely.

A meta-analysis of observational trials found that GnRH agonist therapy and orchiectomy had similar effects on nonfatal CVD events.[63] Consistent positive associations were found between ADT, especially GnRH agonists and orchiectomy, and the occurrence of CVD events. This is in contrast to findings from a previous meta-analysis studying randomized controlled trials. One such study by Nguyen et al[70] performed a systematic review and meta-analysis of randomized trials regarding ADT and CVD mortality, finding no increased risk of CVD death in a pooled analysis. Differences in the results of these studies may be attributable to differences in study design as well as differences in their study target (CVD events vs CVD mortality). Data from observational studies represent a broader population with fewer age and comorbidity restrictions, which can lead to more applicable results to the general population.[63] Further study is required to better assess possible CVD risk associated with various forms of ADT.

TESTOSTERONE IN POSTMENOPAUSAL WOMEN

Coronary artery disease is the leading cause of death in postmenopausal women.[71] Endogenous free testosterone levels in postmenopausal women have been significantly associated with their degree of CAD, independent of BMI and other risk factors, such as diabetes, hypertension, smoking, and hyperlipidemia.[72] The loss of ovarian function after menopause leads to a dramatic fall of estrogen levels, whereas secretion of testosterone remains at the same levels, or may even increase.[72] This rapid decline of estrogen with menopause causes a period of relative androgen excess. An important quantification of this androgen excess, the free androgen index, tends to be a better predictor of many health outcomes, especially CVD ones, compared with testosterone alone.[72] Most (~65%) circulating testosterone is bound to SHBG, and levels of SHBG are increased by estrogen.[72] The free androgen index is calculated as testosterone/SHBG.[72] Therefore, after menopause, the decreased levels of estrogen lead to decreasing levels of SHBG and a higher free androgen index. It has been hypothesized that a relative androgen excess during the menopausal transition may at least partially be responsible for CVD risk in women.

There is a growing body of evidence suggesting that adrenal androgens play an important role in the estrogen/androgen balance during the menopausal transition.[73] Levels of dehydroepiandrosterone sulfate rise distinctly in most women during menopause, and it seems that most if not all of this rise is attributable to the adrenal gland, considering that a similar rise is seen in ovariectomized women.[73] Also, postmenopausal women with adrenal insufficiency have minimal circulating testosterone, with no response to stimulation.[72]

High androgenicity (expressed as a high free androgen index) is associated with an adverse CVD risk factor profile in postmenopausal women; however, firm conclusions about clinical CVD events cannot be drawn due to limitations in study design and scarce or inconclusive longitudinal data.[74] It is currently undetermined whether adrenal androgens have a causal role regarding CVD in postmenopausal women. Existing data from testosterone supplementation studies further suggest that the use of low-dose transdermal testosterone is safe; however, studies examining potential adverse effects were often restricted by short follow-up.[74] Because testosterone therapy is increasingly used for

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postmenopausal women, its long-term effects on CVD risk need further study.[74] According to a panel of researchers presenting at the AACE 24th annual scientific and clinical congress, the benefits of testosterone replacement therapy to treat low testosterone levels in men and women substantially outweigh any risks.[75]

CONCLUSION

Although there is evidence of testosterone deficiency being associated with increased mortality in multiple cohort studies, it remains unclear whether this is a causal relationship or due to low testosterone level being a biomarker of poor overall health.[2] Considering that CVD occurs most commonly in elderly men and that elderly men typically have lower levels of serum testosterone and increased chronic disease burden, there are multiple confounding variables regarding any potential cause and effect of endogenous testosterone levels on CV health. The evidence overall suggests that normal physiologic levels of testosterone are beneficial to the male CV system and that testosterone deficiency is associated with an unfavorable metabolic profile and increased CVD events, such as MI and mortality. Increased IMT, which has been studied as an indicator of atherosclerotic progression, is found to be associated with testosterone deficiency across multiple phenotypically distinct patient populations, including elderly men and obese adolescent females.

The FDA, the AACE/ACE, and the international consensus panel all state that testosterone therapy is safe and reasonable in patients with symptomatic testosterone deficiency (the FDA definition of testosterone deficiency is the only definition that does not include symptoms).[6,13,24] Regarding CAD, multiple studies have found that testosterone therapy is associated with increased time to ischemia. Whereas Malkin et al[12] concluded that low serum testosterone level was an independent parameter that influenced time to mortality, suggesting a possible mortality benefit of testosterone therapy in hypogonadal patients with CAD, Budoff et al[16] found that testosterone therapy was associated with increased total coronary plaque burden in a similar cohort. The ongoing Cardiovascular Trial of The Testosterone Trials will test the hypothesis that testosterone therapy inhibits coronary plaque progression as assessed by serial CCTA.

Although the ideal study to determine a causal effect of testosterone deficiency on CVD events would involve patients undergoing ADT and lacking CVD risk factors, this is a rare cohort that would be difficult to study because ADT is typically used to treat prostate cancer, which often occurs in elderly men with other risk factors for CVD. Whereas ADT has certainly been associated with increased CVD risk in multiple studies, there are also large trials that have been unable to replicate these results, finding no such association between ADT and CVD events. Therefore, no firm conclusion can be drawn at this time as to whether androgen deficiency (or replacement) in men who have been treated for prostate cancer is associated with CVD effects. We agree with the European Association of Urology 2012 prostate cancer guidelines,[59] which state that the evidence regarding ADT and CVD mortality risk is not consistent, and we add that it is inconsistent with respect to CVD events, such as MI, SCD, and stroke. The international expert consensus panel that convened in 2015 concluded that there is a need for a major research initiative to explore the possible cardioprotective benefits of testosterone therapy, implying that there is sufficient evidence regarding the safety of testosterone therapy in hypogonadal men and that the direction of future research should be set toward defining suitable therapeutic options for CVD.

We agree with the current opinions of the AACE/ACE as well as the international expert consensus panel that testosterone treatment should be considered for symptomatic men with clinically confirmed hypogonadism, that there is no compelling evidence that testosterone therapy either increases or decreases CVD risk, and that testosterone therapy for men with testosterone deficiency is effective, rational, and evidence based. Whereas there are associations between androgen excess and CVD in postmenopausal women, there is currently limited evidence to suggest that adrenal androgens have a causal role in CVD in women. The benefits of treatment of low testosterone levels with testosterone therapy in men and women substantially outweigh any risks, according to the current data.

Abbreviations and Acronyms: **6MWT** = 6-Minute Walk Test; **AACE** = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **ADT** = androgen deprivation therapy; **BMI** = body mass index; **BRS** = baroreflex sensitivity; **CAC** = coronary artery calcium; **CAD** = coronary artery disease; **CCTA** = coronary computed tomographic angiography; **CHF** = chronic heart failure; **CV** = cardiovascular; **CVD** = cardiovascular disease; **DVT** = deep vein thrombosis; **EF** = ejection fraction; **FDA** = Food and Drug Administration; **FSH** = follicle-stimulating hormone; **GnRH** = gonadotropin-releasing hormone; **HDL** = high-density lipoprotein; **HF** = heart failure; **HR** = hazard ratio; **hs-CRP** = high-sensitivity C-reactive protein; **IFG** = impaired fasting glucose; **IL** = interleukin; **IMT** = intima-media thickness; **LDL** = low-density lipoprotein; **LH** = luteinizing hormone; **MI** = myocardial infarction; **OR** = odds ratio; **PE** = pulmonary embolism; **RCT** = randomized controlled trial; **ROS** = reactive oxygen species; **SCD** = sudden cardiac death; **SHBG** = sex hormone binding globulin; **TNF** = tumor necrosis factor; **TOM** = Testosterone in Older Men With Mobility Limitations

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