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The role of testosterone in cardiovascular health: benefits and risks of replacement therapy

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Abstract

Testosterone, the primary male sex hormone, significantly impacts cardiovascular health. Produced mainly in the testes, its levels decline with age, leading to increased risks of cardiovascular diseases, sexual dysfunction, and metabolic disorders. This paper examines testosterone's dual role in the cardiovascular system. Low levels are linked to increased risks of heart failure (HF) and coronary artery disease (CAD), while testosterone replacement therapy (TRT) can improve heart function, exercise tolerance, and metabolic health. However, supraphysiological doses or long-term therapy may cause pathological heart hypertrophy and vascular complications. Testosterone influences cardiomyocyte apoptosis, calcium regulation, and oxidative stress reduction, with anti-inflammatory effects shown to lower pro-inflammatory cytokine levels. Studies demonstrate TRT's benefits in reducing cholesterol, blood pressure, and ischemic episodes in CAD patients, but conflicting data exist regarding its association with myocardial infarction risk. Additionally, testosterone's effects vary in different cardiomyopathies, showing both protective and harmful outcomes. This review underscores the need for carefully tailored TRT to balance the benefits of maintaining optimal testosterone levels while minimizing cardiovascular risks.

Running title: Cardiac dysfunction and testosterone replacement therapy

Keywords: testosterone replacement therapy, heart failure, arteriosclerosis, cardiomyopathies

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Introduction

Testosterone is the primary male sex hormone, produced and secreted mainly in the testes. In the blood, it exists in two forms: bound to androgen-binding globulin or free (1%-2%). It is the unbound fraction that exhibits significant biological activity [1]. The history of testosterone began in 1929 when Adolf Butenandt first isolated it. Over time, synthetic forms were developed, and the idea of treating with exogenous testosterone was implemented more than 75 years ago [2,3]. Due to the reduction in testicular volume and declining efficiency of their function with age, testosterone production decreases by 1-2% per year after the age of 50, following its peak in the 2nd–3rd decade of life [4,5]. Testosterone deficiency can be associated with sexual dysfunction and an increased risk of cardiovascular diseases [1,6]. Testosterone can have both positive and negative effects on the heart and vascular system. This hormone reduces symptoms associated with angina, accelerates repair and healing processes in the heart after a myocardial infarction, and improves functionality in male patients with HF [7]. Data from the Center for Medicare and Medicaid Services indicate that topical testosterone is most commonly prescribed by endocrinologists (60.4%) and urologists (53.5%), while injections are primarily prescribed by family physicians (59.82%) and internists (50.69%) [8]. The same database reports that between 2016 and 2019, the number of physicians prescribing testosterone increased by approximately 29%, while the number of prescriptions issued and used by patients to obtain testosterone increased by about 55% [9]. In 2014, testosterone prescriptions were most commonly written for patients with conditions such as hypogonadism (48%), fatigue (18%), erectile dysfunction (15%), depression (4%), and psychogenic sexual dysfunction (1%) [10].

The protective effects of testosterone on cardiac structure, function, and the cardiovascular system

Several intercellular mechanisms result in testosterone having cardioprotective functions, including its role in reducing apoptosis, maintaining calcium homeostasis, and mitigating oxidative stress in cardiomyocytes[11–13].Low levels of testosterone have been linked to an increased risk of cardiovascular diseases and reduced survival in men [14]. Oxidative stress is known to cause heart dysfunction [15]. Superoxide dismutase and glutathione peroxidase are enzymes that reduce harmful reactive oxygen species (ROS) [16,17]. It has been shown that castrated mice had lower levels of those antioxidative enzymes in the myocardium [13]. They also had mitochondrial DNA deletion mutations and higher levels of malondialdehyde (an aldehyde formed during polyunsaturated fatty acids oxidation [18]. Those effects were not observed in mice with testosterone therapy suggesting that testosterone therapy decreases oxidative stress [13]. Cardiomyocyte apoptosis which is linked to oxidative stress plays an major role in HF [19]. Studies show that castrated rats after myocardial infarction had decreased levels of markers that play roles in inflammation and apoptosis: caspase-1, caspase-3, and caspase-11 expression, as well as TNF-α, IL-1β, IL-6, and p38 MAPK. p38 MAPK is activated by stress stimuli, leading to the production of inflammatory cytokines like TNF-α and IL-1β. Caspase-11 activates caspase-1, which in turn matures IL-1β, while caspase-3 is involved in apoptotic signaling. The markers increase in response to ischemia-reperfusion injury and oxidative stress. They also had increased expression of the anti-apoptotic protein Bcl-2 compared to non-castrated rats. However, low doses of testosterone have been shown to have an anti-apoptotic effect on myocardial cells. Male rats given low doses of testosterone exhibited lower caspase-3 expression, better heart function, and lower mortality after myocardial infarction [11]. Additionally, testosterone has anti-apoptotic effects in other organs, including the prostate, where it reduces H2O2-induced apoptosis[20]. Testosterone induces apoptosis via an extrinsic pathway in vascular smooth muscle cells and does not promote the intrinsic pathway, as it does not trigger cytochrome-c release from mitochondria to the cytosol [11]. Calcium ions increase during ischemia and early reperfusion lading to incresed ATP consumption and apoptosis resulting to myocardial damage [21,22]. Testosterone affects contractile function in the heart by playing a role in maintaining calcium (Ca^{2+}) homeostasis and preventing pathological calcium overload. This is achieved by activating L-type calcium channels, which increase calcium influx into the cell [12]. In rats with gonadectomy, testosterone has completely reversed hypercontractility that was caused by cardiomyocyte systolic Ca^{2+} transient [23]. Testosterone has anti-inflammatory properties. It correlates negatively with C-reactive protein level [24]. Lower androgen levels are associated with decreased inhibition of pro-inflammatory cytokines [25]. Testosterone treatment reduces the production of TNFα, IL-1β and IL-6 by antigen-presenting cells. However, antigen-presenting cell preserve their ability to produce pro-inflammatory cytokines after testosterone treatment when stimulated by recombinant human interferon-γ and lipopolysaccharide [26]. Testosterone also increases IL-10 (anti-inflammatory cytokine) [27].

Low testosterone levels have been linked to the development of hypertension, a key risk factor for chronic heart disease. [28,29] Elevated blood pressure contributes to increased vascular resistance, which plays a central role in cardiovascular pathology. One of the mechanisms involved includes the

activity of non-receptor tyrosine kinases. They mediate vascular contraction and hypertrophy which are crucial to contributing to the heightened vascular resistance observed in hypertension. Testosterone regulates those processes in male animals' vascular smooth muscle cells [30].

Cardiac remodeling is a process of structural and functional changes in the heart which can precipitate HF and various cardiovascular complications. Epidemiological studies show that low testosterone is linked with higher rates of atherosclerosis, CAD and adverse cardiovascular events. [31,32] It was also correlated with more severe HF, as well as higher NYHA class, reduced exercise capacity and worse clinical prognosis and mortality [33] Hypogonadism is connected to metabolic derangements such as insulin resistance, type 2 diabetes, dyslipidemia and hypertension. All these conditions stimulate oxidative stress, impair cellular respiration and alter lipid metabolism in cardiac tissue, thus promoting cardiac remodeling. [34,35]. Excess adipose tissue produces pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, leading to chronic inflammation. Such inflammatory environment promotes activation of cardiac fibroblasts, leading to increased deposition of extracellular matrix proteins and interstitial fibrosis [36,37]. Animal studies associate low testosterone with mitochondrial dysfunction in cardiac cells by downregulating important regulators of mitochondrial biogenesis, for instance PGC-1α, NRF-1/2, and TFA, leading to decreased DNA replication and protein synthesis in the mitochondria. It also alters the balance of mitochondrial fission by affecting Drp1, Mfn1 and OPA1 proteins, causing accumulation of defective and morphologically abnormal mitochondria [38,39]. Dysfunctional mitochondria generate excess ROS, causing oxidative damage to DNA, proteins and lipids, triggering myocyte apoptosis and hypertrophy, which is further exacerbated by impaired mitochondrial calcium homeostasis [40]. Another study on aging mice indicates that chronic testosterone deficiency led to maladaptive electrical remodeling, including prolonged action potentials and increased arrythmia risk, mainly due to late inward sodium current and promotion of triggered activity in ventricular myocytes[41]. Contrary to that, there are some models suggesting opposite effects of testosterone deficiency. In rat models, low testosterone (induced via castration) attenuated adverse cardiac remodeling after myocardial infarction. These animals had reduced myocyte hypertrophy and preserved contractility compared to non-castrated rats [42].

Characteristics of major heart diseases

HF is typically defined as a syndrome of clinical features that include both structural and functional heart abnormalities, usually associated with reduced cardiac output and/or increased intracardiac pressure [43]. The pathophysiology of HF is complex and involves both systolic and diastolic dysfunction of the left ventricle, along with the activation of compensatory mechanisms [44,45]. In the early stages of HF, compensatory responses such as neurohormonal activation and stimulation of the sympathetic nervous system are initiated. Although these mechanisms initially serve to counterbalance cardiac dysfunction, they ultimately contribute to disease progression and the emergence of clinical symptoms [46]. HF is classified into different types based on the left ventricular ejection fraction (LVEF). In heart failure with reduced ejection fraction (HFrEF), defined by LVEF below 40%, systolic dysfunction plays a central role, often associated with valvular abnormalities and loss of cardiomyocytes, for example, as a consequence of myocardial infarction [47,48]. Another subgroup includes patients with heart failure with preserved ejection fraction (HFpEF), characterized by an LVEF greater than 50%. This form is primarily associated with diastolic dysfunction of the left ventricle, leading to impaired ventricular filling due to myocardial stiffness resulting from fibrosis [49,50]. In HFrEF, diastolic dysfunction may also be present, particularly in the context of cardiomyocyte loss – such as following myocardial infarction – and structural abnormalities of the cardiac valves [48]. Approximately 64 million people worldwide suffer from this condition. In developed countries, around 1.5% of the adult population is affected by HF [51]. The study by Di Lodovico et al. estimates that testosterone deficiency occurs in approximately 25–56% of patients with HF [33]. A prospective observational study investigating the relationship between testosterone levels and HF found that low testosterone levels were associated with hypoalbuminemia, edema, anemia, cardiac muscle cell dysfunction and damage, as well as poorer prognosis in men with HF [52].

CAD is a condition where the coronary arteries, responsible for supplying oxygen-rich blood to the heart muscle, become narrowed or blocked. This is typically caused by the buildup of plaque [53]. Endothelial dysfunction (ED) plays a pivotal role in atherosclerotic processes and is considered an early marker of atherosclerosis [54]. ED is a state of impaired balance between vasoconstrictive and vasodilatory factors, which fosters a prothrombotic environment [55]. Cardiovascular risk factors such as stress, dyslipidemia, hypertension, and smoking induce inflammatory responses within the endothelium, leading to decreased synthesis of nitric oxide (NO) and increased production ROS, which contribute to oxidative stress [56,57]. This state facilitates the accumulation and modification of low-density lipoproteins (LDL) within the subendothelial space. This, in turn, stimulates the transformation of macrophages into foam cells, which secrete cytokines and growth factors. These substances promote the

proliferation of the extracellular matrix, resulting in the formation of atherosclerotic plaques [58]. Disturbances in glucose and lipid metabolism constitute significant risk factors for CAD. Testosterone plays a key regulatory role in these metabolic processes [59–61]. Studies have demonstrated a strong association between testosterone deficiency and reduced insulin sensitivity, as well as an increased risk of developing type 2 diabetes mellitus [62,63]. estosterone stimulates the translocation of glucose transporter type 4 (GLUT4) receptors to the surface of muscle cells and adipocytes, thereby enhancing glucose uptake and contributing to lower blood glucose levels [64,65]. Furthermore, analyses have shown a correlation between low testosterone levels and elevated concentrations of LDL cholesterol, total cholesterol, and triglycerides [62]. Testosterone enhances the activity of hormone-sensitive lipase and increases the capacity for fatty acid oxidation, thereby promoting lipolysis. [66].

Cardiomyopathies consist of a range of heart muscle disorders characterized by structural and functional abnormalities of the ventricular myocardium, which are not attributable to abnormal loading conditions or obstructive CAD [67]. Hypertrophic cardiomyopathy (HCM) is caused by abnormal increase in heart muscle cells. Frequently caused my genetic factors it leads to disorganized myocytes. Dilated cardiomyopathy (DCM) is characterized by ventricular enlargement and weakened contraction, often progressing to HF. Restrictive cardiomyopathy (RCM) caused by genetic factors leading to ventricle stiffens that impaired filling. In arrhythmogenic right ventricular cardiomyopathy (ARVC) heart muscle is replaced with fibrofatty tissue [68]. Men with idiopathic DCM and chronic HF consistently show significantly lower free and total testosterone in comparison with healthy controls. This reduction is likely related to chronic disease processes and is frequently accompanied by decrease in other anabolic hormones such as growth hormone and IGF-1. Chronic HF and DCM may suppress the hypothalamic-pituitary-gonadal axis, leading to hypogonadism. [69,70]. Although low testosterone is linked to worse quality of life and more severe depressive symptoms in DCM, studies following men with DCM found that no independent association was found between testosterone deficiency and adverse outcomes such as death, transplantation or hospitalization rates in stable, well treated patients [69,71]. As far as HCM is concerned, the reviewed studies directly link low testosterone neither to the development nor progression of HCM. Experimental studies show that testosterone can induce hypertrophy of cardiac cells through pathways involving AMPK, AR and mTORC1/S6K1 signalling. However, these effects are generally observed with normal or high testosterone levels, not low levels [72,73]. Cardiac fibrosis is a central feature in the development and progression of restrictive cardiomyopathy (RCM), a rare heart muscle disorder characterized by impaired ventricular filling due to increased myocardial stiffness. Physiological levels of testosterone reduce cardiac fibroblast migration, proliferation, myofibroblast differentiation, and collagen production. Testosterone attenuates the activation of transforming growth factor-β (TGF-β) and angiotensin II signaling pathways, both of which are central to promoting fibrosis. This is achieved by reducing phosphorylation of Akt, mTOR, 4E-BP1, P38, and Smad 2/3, and by increasing matrix metalloproteinase-2 activity, which helps break down excess collagen [74]. Although there is a lack of direct evidence, testosterone deficiency may have an inhibitory effect on mentioned pathways, therefore causing fibrosis.

Cardiovascular consequences of testosterone deficiency

Testosterone deficiencies occur when the body is unable to produce adequate amounts of the hormone, leading to a decline in overall functionality. Despite aging being associated with decreasing testosterone levels, more than 80% of men maintain normal levels into old age [75]. Low testosterone levels are typically linked to poor prognosis and an increased risk of fatal cardiovascular complications [76]. According to the American Urological Association, low testosterone is associated with a higher likelihood of severe cardiovascular complications, such as myocardial infarction and stroke, and is considered a risk factor for atherosclerosis-related diseases [77]. Other studies suggest that low testosterone may be linked to hypertension, although it is unclear whether it is the cause or consequence (28,29) Testosterone therapy in men suffering from testosterone deficiency may help reduce fatal incidents related to harmful cardiovascular complications, likely due to testosterone's ability to improve metabolic processes in the body and reduce inflammation [78,79]. Furthermore, in women with fraction HFrEF, testosterone deficiency significantly impacts mortality and complication risks [80]. Cohort studies on androgen deprivation therapy, commonly used in prostate cancer patients, have shown an increased risk of cardiovascular disease [81–85]. Some of these studies, along with the meta-analysis by Liang et al., indicate that the most common complications include myocardial infarction, HF, and stroke [82,83,86].

Cardiovascular consequences of excessive testosterone levels

Both testosterone deficiency and excess can lead to undesirable complications affecting both the heart and the vascular system [87]. Many of these

TABLE 1 Summary of clinical studies regarding testosterone supplementation in patients with HF

	STUDY	YEAR	METHODS	N	AIM	OUTCOMES
1.	Tao et al.	2020	Testosterone administration in randomized clinical trial	170	Evaluation of the effect of testosterone supplementation on exercise tolerance and heart function in patient with chronic HF	Testosterone administration is not associated with significantly improved exercise tolerance, cardiac function and clinical outcome
2.	Navarro--Peñalver et al.	2018	Testosterone administration via intramuscular injection (1000mg) every 3 months for 12 months and measuring functional capacity via NYHA class, Framingham score, Minnesota Living Heart Failure Questionnaire, 6-minute walk test, or LVEF and N-terminal pro-B-type natriuretic peptide levels compared to placebo	29	Evaluation of the effect of testosterone supplementation in patients suffering from HFrEF and testosterone deficiency	Therapy was not associated with any major clinical improvement
3.	Toma et al.	2012	Testosterone administration and measuring functional capacity via 6-minute walk tests	198	Evaluation of the effect of testosterone supplementation on exercise tolerance in patient with stable, chronic HF	Therapy was associated with a apparent improvement in exercise capacity compared with placebo
4.	Wang et al.	2016	Testosterone administration and measuring exercise capasity, muscle strength, ECG indicators and hemodynamic parameters	393	Evaluation of the effect of testosterone supplementation on clinical benefits and quality of life in patients with chronic, stable HF	Therapy was associated with an improvement in exercise capacity, muscle strength and ECG indicators but there was no apparent changes in LVEF, blood pressure, and and N-terminal pro-B-type natriuretic peptide levels
5.	Mirdamadi et al.	2014	Testosterone administration via intramuscular injection (250mg) every 4 weeks for 12 weeks and measuring functional capacity, body weight, hemodynamic parameters compared to placebo	50	Evaluation of the effect of testosterone supplementation on clinical benefits as well as cardiovascular improvements and quality of life in patients with chronic, stable HF	Therapy was associated with a apparent improvement in exercise capacity and quality of life compared with placebo
6.	Lellamo et al.	2010	Testosterone administration via transdermal patch for 6 months and measuring functional capacity via 6-minute walk tests, cardiopulmonary exercise test, echocardiogram, quadriceps maximal isometric voluntary contraction, dynamic quadriceps isokinetic strength, and insulin resistance assessment by homeostasis model	36	Evaluation of the effect of testosterone supplementation on exercise tolerance and insulin resistance in female patients with chronic HF	Therapy was associated with a apparent improvement in exercise capacity, insulin resistance, and muscle strength in women with advanced chronić HF
7.	Caminiti et al.	2009	Testosterone administration via intramuscular injection (1000mg) every 6 weeks for 12 weeks and measuring functional capacity via 6-minute walk tests, cardiopulmonary exercise test, echocardiogram, quadriceps maximal isometric voluntary contraction , and isokinetic strength and BRS assessment	76	Evaluation of the effect of testosterone supplementation on exercise tolerance, muscle strength, glucose metabolism, and BRS in men with moderately severe chronic HF	Therapy was associated with a apparent improvement in exercise capacity, muscle strength, glucose metabolism, and BRS

complications are associated with structural damage to the heart muscle, an increased risk of heart attack, and elevated blood pressure [88]. Doctors typically do not prescribe testosterone doses that raise levels to supraphysiological ranges in patients with deficiency due to the increased risk of cardiovascular complications [87,89,90]. The duration of testosterone therapy can result in different types of myocardial hypertrophy. Short-term therapy may lead to physiological and non-harmful hypertrophy, whereas long-term therapy can result in severe and life-threatening cardiac complications related to pathological hypertrophy [91]. Studies also indicate that supraphysiological testosterone therapy may cause vascular problems [87] particularly affecting the vascular endothelium [90], further contributing to increased cardiovascular risk.

The use of testosterone therapy in patients with preexisting cardiovascular disease

Heart failure

Testosterone supplementation in HF patients has yielded mixed results. Both a 2018 and a 2020 study concluded that testosterone therapy did not produce significant benefits [92,93]. However, a meta-analysis [94] and other studies [95–98] suggested that this therapy may have positive effects, particularly in improving exercise tolerance, increasing muscle strength, and reducing insulin resistance in both men and women. Long-term use of testosterone derivatives may contribute to the development of HF through pathological hypertrophy and fibrosis of the myocardium. This process is primarily driven by direct stimulation of androgen receptors in cardiomyocytes and activation of the renin–angiotensin–aldosterone (RAA) system, which subsequently leads to hypertension, chronic inflammation, and adverse cardiac remodeling. Despite an increase in muscle mass, myocardial contractility does not improve due to predominant collagen deposition rather than an increase in functional cardiomyocyte number. This contributes further to arrhythmias and impaired systolic function of the heart [99]. Moreover, disturbances in testosterone levels – specifically, testosterone deficiency in men (particularly free testosterone) and relatively elevated testosterone levels in postmenopausal women (reflected, for instance, in a higher testosterone-to-estradiol ratio) – have both been associated with an increased risk of HF, particularly HFrEF. This relationship has been confirmed by large population-based studies such as the ARIC (Atherosclerosis Risk in Communities) and MESA (Multi-Ethnic Study of Atherosclerosis) cohorts, which demonstrated that abnormal androgen concentrations may adversely affect cardiac function in a sex- and age-dependent manner [100]. In contrast, an analysis of prospective cohort data from the UK Biobank suggests that higher levels of free androgens – including free testosterone – are associated with a lower risk of developing HF in men and postmenopausal women, indicating a potentially protective effect in these populations. However, a different pattern was observed in premenopausal women, in whom higher levels of free estradiol were correlated with an increased risk of HF [101]. **Table 1** summarizes data on clinical trials of testosterone supplementation in patients with heart failure.

Coronary artery disease

Elderly men with higher levels of testosterone are known to have reduced chances of cardiovascular events [102]. Also, men with lower testosterone levels have increased risk of CAD compared to men with higher plasma testosterone levels [103]. There are several mechanisms in which testosterone affects patients with CAD. In men with hypogonadism who received TRT for up to 8 years the scientifically significant decrease in fasting glucose, triglycerides: HDL ratio, CRP and total cholesterol levels were noted. Both systolic and diastolic blood pressure as well as pulse were significantly reduced [104]. Another study is consistent with those findings showing a reduced cholesterol level, decreased HOMA-IR and triglycerides level in patients with TRT compared to the placebo group. Moreover, acute testosterone administration is shown to reduce the number of ischemic episodes and frequency of angina attacks in patients with CAD [105]. A 14-week-long study in men with CAD showed an increase in time to 1-mm ST-segment depression in patients with transdermal testosterone patches [106]. Testosterone therapy has been studied in patients with CAD and hypogonadism. One 8-year study reported no major adverse cardiovascular events in treated individuals [104]. While some research suggests an increased risk of myocardial infarction [107] and prostate enlargement [108] associated with testosterone use. However, other studies contradict these findings, showing no elevated risk of MI [109]. nor PSA level changes [106].

Cardiomiopathies

In ARVC male patients, the levels of plasma testosterone are higher compared to those in healthy males. Additionally, testosterone levels are not associated with baseline cardiac function [110]. However, another study linked HF in men caused by DCM with lower testosterone concentrations [69]. Also, patients with African endomyocardial fibrosis that causes restrictive cardiomyopathy are shown to have lower testosterone levels than a control group [111].

Risks associated with testosterone replacement therapy: a review of clinical studies

TRT is commonly used in men with symptomatic hypogonadism; however, its effects on the cardiovascular system remain controversial, as results from clinical trials and meta-analyses to date have been inconsistent, complicating the formulation of clear clinical guidelines [112]. Some evidence suggests that TRT may increase the risk of myocardial infarction, particularly in older men or those with pre-existing cardiovascular risk factors. For instance, in a retrospective study by Finkle et al., the risk of myocardial infarction more than doubled within 90 days of initiating TRT in men over the age of 65 [107]. Similar conclusions were drawn by Vigen et al., who observed an increased risk of myocardial infarction, stroke, and all-cause mortality among patients with low testosterone levels who were treated with TRT [113]. Conversely, a 2021 meta-analysis including eight studies (six observational and two randomized trials) did not demonstrate a significant increase in myocardial infarction risk in the TRT group compared to the control group, although the authors emphasized the high heterogeneity of the data and highlighted the need for further randomized trials with longer follow-up periods [114]. Another study, comprising 15 epidemiological investigations and 93 randomized clinical trials, found no conclusive impact of TRT on cardiovascular events. However, potential benefits were observed in men with obesity (BMI > 30 kg/m^2), though this effect disappeared in analyses limited to high-quality studies [115]. Furthermore, the large randomized traverse trial, which enrolled 5,246 men with hypogonadism and cardiovascular risk, assessed the use of transdermal testosterone gel (1.62%) over approximately 22 months. The study found no superiority of TRT over placebo in reducing major cardiovascular events; however, it did reveal a significantly higher incidence of atrial fibrillation, pulmonary embolism, and acute kidney injury in the TRT group [116].

The outcomes of TRT studies vary significantly depending on the mode of administration, dosage, and characteristics of the study population, all of which influence both treatment efficacy and the adverse event profile. This highlights the need for individualized therapy that takes into account pharmacokinetics, patient tolerance, and the potential risks of cardiovascular and hematological complications [117]. Nevertheless, due to considerable methodological limitations in most existing studies on TRT — including their retrospective design, short follow-up duration, and population heterogeneity — it is currently not possible to definitively determine the long-term safety of testosterone therapy. This underscores the urgent need for well-designed, multicenter, long-term randomized controlled trials that address patient diversity, as well as different routes of administration, dosages, and durations of treatment [1].

Conclusions

Many studies highlight the beneficial effects of testosterone on the heart and blood vessels, such as reducing symptoms of angina, improving heart function after a heart attack, and increasing exercise tolerance in patients with HF. These effects are attributed to testosterone's role in calcium homeostasis regulation, its anti-inflammatory properties, and its influence on metabolic processes. As a result, testosterone therapy may provide significant benefits in treating cardiovascular diseases in men with testosterone deficiency. However, excessive testosterone supplementation leading to supraphysiological hormone levels is associated with serious complications, including pathological myocardial hypertrophy and vascular damage. Despite these potential benefits and risks, research findings on testosterone therapy remain partially contradictory, particularly regarding its long-term effects on cardiovascular health, underscoring the need for further investigation. Future research should focus on several key aspects. First, a better understanding of the molecular mechanisms of testosterone's effects on the heart and vascular system is needed, particularly its role in apoptosis, calcium homeostasis, and anti-inflammatory processes. Another critical area of study is the long-term effects of testosterone therapy to better assess its safety in relation to cardiovascular complications. Optimizing hormonal therapy for patients with testosterone deficiency, while considering individual patient needs, is essential to maximize health benefits while minimizing risks. Additionally, the role of testosterone in women, particularly those suffering from HF, remains poorly understood, as there is a lack of data on its impact on their cardiovascular system. These studies could contribute to improving the effectiveness of testosterone therapy and enhancing the understanding of its potential benefits and risks, which is crucial for advancing medicine in the context of cardiovascular disease treatment.

Ethical approval
This study is not related to either human or animal use.

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