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REVIEW ARTICLE

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Late-onset hypogonadism: *Reductio ad absurdum* of the cardiovascular risk-benefit of testosterone replacement therapy

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Abstract

Background: Low testosterone (T) level is considered a marker of poor cardiovascular health. Ten years ago, the Testosterone in Older Men with Mobility Limitations (TOM) trial was discontinued due to a higher number of adverse events in men receiving T compared with placebo. Since then, several studies have investigated the risks of T replacement therapy (TRT) in late-onset hypogonadism (LOH).

Objective: To review the mechanism by which TRT could damage the cardiovascular system.

Materials and methods: Comprehensive literature search of recent clinical and experimental studies.

Results: The mechanisms of T-mediated coronary vasodilation were reviewed with emphasis on calcium-activated and ATP-sensitive potassium ion channels. We showed how T regulates endothelial nitric oxide synthase (eNOS) and phosphoinositide 3-kinase/protein kinase B/eNOS signaling pathways in vessel walls and its direct effects on cardiomyocytes via β1-adrenergic and ryanodine receptors and provided data on myocardial infarction and heart failure. Vascular smooth muscle senescence could be explained by the modulation of growth factors, matrix metalloproteinase-2, and angiotensin II by T. Furthermore, leukocyte trafficking, facilitated by changes in TNF-α, could explain some of the effects of T on atheromatous plaques. Conflicting data on prothrombotic risk linked to platelet aggregation inhibition via NO-triggered arachidonate synthesis or increased aggregability due to enhanced thromboxane A in human platelets provide evidence regarding the hypotheses on plaque maturation and rupture risk. The effects of T on cardiac electrophysiology and oxygen delivery were also reviewed.

Discussion: The effects of TRT on the cardiovascular system are complex. Although molecular studies suggest a potential benefit, several clinical observations reveal neutral or occasionally detrimental effects, mostly due to confounding factors.

Conclusions: Attempts to demonstrate that TRT damages the cardiovascular system via systematic analysis of the putative mechanisms led to the contradiction of the

initial hypothesis. Current evidence indicates that TRT is safe once other comorbidities are addressed.

KEYWORDS

aging, androgen, heart failure, myocardial infarction, testosterone, thromboembolism

1 | INTRODUCTION

It is well-known that both total and bioavailable testosterone (T) levels slightly and progressively decrease with aging in men, independently from other confounding factors such as obesity, illness, medications, cigarette smoking, or alcohol intake.[1,2] The rate of decline has been estimated to be 0.8%-2% per year after 40 years of age.[3] Indeed, according to the main observational studies, 12%-38.7% of men aged ≥ 40 years show T deficiency,[1,4-6] with the incidence progressively increasing from 20% in men over 60 years to 50% in those over 80 years.[1] Furthermore, a proportion of these subjects develop symptoms related to low T levels, such as poor morning erection, low libido, erectile dysfunction, inability to perform vigorous activities, depression, and fatigue.[7] In this population, the presence of at least three sexual symptoms associated with low T levels leads to the diagnosis of late-onset hypogonadism (LOH),[7] with a prevalence of 2.1%-6%.[4,6,7]

Older men with LOH can be differentiated based on hormone measurements, clinical features, and predisposing risk factors into the following functional categories: primary hypogonadism, which is strongly associated with age, and secondary hypogonadism, which is related to obesity and is potentially reversible.[8] A third category is represented by compensated or subclinical hypogonadism, which should be considered as a specific clinical entity.[8,9] These findings imply that age-related decline in T, mainly caused by testicular failure,[10,11] is not the only factor underlying the pathogenesis of LOH, which also involves hypothalamic-pituitary function impairment.[12] Subsequently, LOH can be defined as mixed or combined hypogonadism.[13,14] In this regard, comorbidities and lifestyle factors play a major role both independently and in combination with aging.[2,15] In particular, metabolic syndrome and type 2 diabetes dramatically contribute to hypothalamic-pituitary-testicular axis suppression and can in turn be promoted by low T levels themselves in a bidirectional relationship.

Moreover, metabolic syndrome and type 2 diabetes are well-known risk factors of cardiovascular (CV) disease.[17,18] They may increase the risk of premature death in these patients. However, it is now understood that LOH beyond the worst metabolic profile is associated with CV morbidity and mortality per se.[19-21]

The unfavorable metabolic profile of patients with LOH could be restored by improvements in lifestyle[22] as well as by T replacement therapy (TRT), which both contributes to a decrease in abdominal fat, total cholesterol and triglyceride levels, as well as fasting glycemia and insulin resistance.[23,24] Therefore, the metabolic-related CV risk of these subjects might be reduced.[19,25] Moreover, some studies have demonstrated a protective effect of TRT against CV events and mortality in older men with T deficiency at high CV risk.[26-28] Nonetheless, the safety of TRT in LOH is still controversial: Some studies on CV outcomes have shown an increase in CV adverse events.[29-31] The Testosterone in Older Men with Mobility Limitations (TOM) trial evaluated the safety and efficacy of TRT in men aged ≥ 65 years with T deficiency and mobility limitation.[29] However, this study was prematurely discontinued due to a higher rate of CV events in the T group than in the placebo group. The results of this trial sparked the debate of the CV safety of TRT as it had several flaws. First, since the primary outcome of the trial was the change in maximal voluntary muscle strength from baseline until after high-dose TRT, the study was not sufficiently powered to evaluate the CV safety of TRT. Second, the study population comprised elderly men with a mean age of 74 and with significantly limited mobility; in addition, the majority of subjects suffered from several chronic illnesses, including preexisting heart disease. Third, ethnicities as well as the baseline characteristics were different between the two groups, with a higher rate of hypertension, dyslipidemia, and statin use in the T group than in the placebo group. Finally, some of the reported adverse CV events should have been considered as minor phenomena, which could have been dependent on the baseline characteristics of the population. The results of two subsequent observational studies[30,31] resulted in the Food and Drug Administration (FDA) restricting the indications for TRT, warning against the possible risk of myocardial infarction and strokes.[32] In line with this view, the current Endocrine Society guidelines suggest individualized TRT only in men aged 65 years or older with symptomatic T deficiency after providing a detailed explanation regarding the potential risks and benefits of TRT.[14] More recently, the European Academy of Andrology (EAA) guidelines for men with functional hypogonadism have underlined the current lack of conclusive long-term data on the CV risk of TRT,[33] following European Medicines Agency position,[34] and suggest TRT for hypogonadal symptomatic men with sexual or erectile dysfunction.[33]

Assuming that T is harmful to the CV system, this review aimed to examine the putative detrimental mechanisms that could be involved in the increased CV risk of patients with LOH undergoing TRT. To this end, all putative mechanisms by which TRT may cause adverse CV events (Figure 1) were analyzed by first presenting the clinical evidence and by then examining the molecular mechanism pathways targeted by androgens.

2 | METHODS

A Medline search for articles published in English from inception until April 22, 2020, was performed using the following keywords: “late-onset hypogonadism,” “hypogonadism,” “testosterone,”

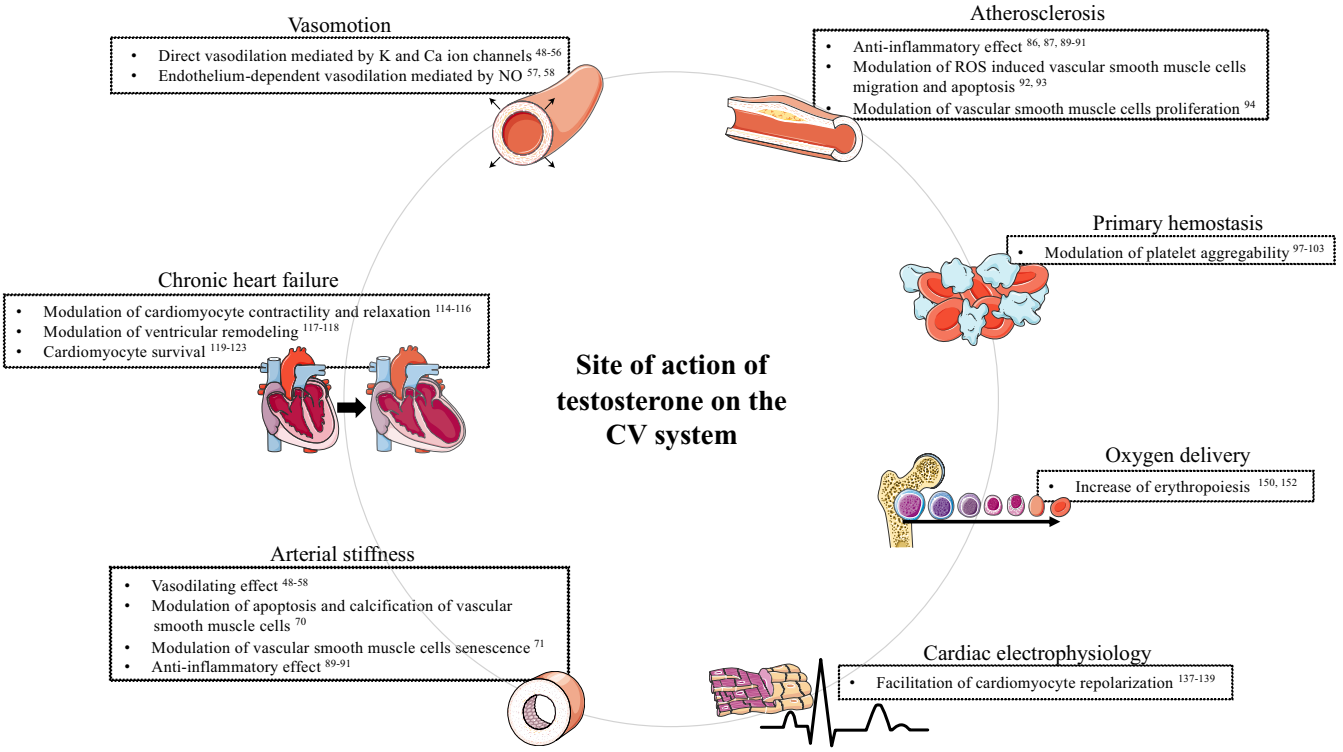

FIGURE 1 Summary of testosterone cardiovascular (CV) effects. Created with images adapted from SMART—Servier Medical Art (http://smart.servier.com), licensed under a Creative Common Attribution 3.0 License (https://creativecommons.org/licenses/by/3.0)

"cardiovascular," "angina," "vasoconstriction," "vasodilation," "arterial stiffness," "atherosclerosis," "hemostasis," "platelet aggregability," "thrombosis," "ventricular," "repolarization," "heart failure," and "erythropoiesis." Keywords were properly combined with Boolean operators to optimize the search.

2.1 | Coronary artery vasomotion

The first evidence of the beneficial effects of T for the treatment of angina pectoris dates back to the 1940s.[35] More recent research has shown that T administration has a beneficial effect on exercise-induced myocardial ischemia in men with coronary artery disease.[36-41] The anti-ischemic effect is achieved both in acute[36,37] and chronic administration.[38-41] The response to T is greater in patients with lower serum T levels than in those with higher serum T levels,[37-39] implying that coronary arteries are more sensitive to T in men with a more severe degree of T deficiency. However, the beneficial effect of T on exercise-induced myocardial ischemia has also been demonstrated in men with normal plasma T concentrations.[37] The beneficial effect of T on myocardial ischemia persists for at least 12 months and is maintained without tachyphylaxis as long as the treatment is continued.[40]

Evidence suggests that the increased angina threshold after T administration in men with coronary artery disease is caused by vasodilation of coronary arteries. The vasodilatory effects of T on coronary arteries have been investigated in both preclinical[42-44] and clinical studies.[45] Intracoronary administration of the physiological concentrations of T in eugonadal men with coronary artery disease induces a prompt (within 2-3 minutes) artery dilation up to 4.5% and increases coronary blood flow up to 17.4% following acetylcholine-induced contraction.[45]

In summary, clinical studies have shown the favorable effects of short- or long-term T treatment on exercise-induced cardiac ischemia and coronary vasomotion. However, the exact mechanism of action by which T exerts its effects on coronary vasculature remains unknown.

A non-genomic action is suggested by the rapid-onset effect on vasodilation.[36,37,45] In vivo animal models as well as in vitro models have shown that T induces coronary vasodilation by an endothelium-independent mechanism and modulates the activity of potassium and calcium channels on the surface of vascular smooth muscle cells.[46,47] In particular, T stimulates the opening of large-conductance calcium-activated potassium ion channels,[48-50] voltage-sensitive potassium ion channels,[50] and ATP-sensitive potassium ion channels[51] and, more importantly, inactivates L-type calcium ion channels.[52-54] In addition, it may cause vasodilation via the inhibition of intracellular calcium influx via store-operated calcium channels.[55] The mechanism of the endothelium-dependent action of T on vascular cells includes long-term genomic effects mediated by the androgen receptor (AR); these include an increase in hydrogen sulfide production, which in turn induces vasodilation via TRPV4 and large-conductance calcium-activated potassium ion channels.[56] Furthermore, an increase in the expression of endothelial nitric oxide synthase (eNOS) results in an increase in nitric oxide (NO) production.[57] Moreover, T has been

demonstrated to increase eNOS activity via rapid AR-dependent activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/eNOS signaling pathway (Table 1).[58]

2.2 | Peripheral arterial stiffness

Existing evidence has recognized increased arterial stiffness, defined as an increased resistance to deformation or decreased elastic compliance, as a predictor of CV events and mortality.[59] Stiffening of the arterial tree increases cardiac afterload and lowers diastolic pressure, thereby altering the transmural distribution of myocardial blood flow. This results in a decrease in subendocardial perfusion during ventricular contraction, eliciting subendocardial ischemia, regardless of the presence of coronary artery stenosis.[60]

Several studies have demonstrated an independent inverse association between T levels and arterial stiffness.[61-66] However, this has been confirmed in specific populations, such as older hypogonadal men [63,64] and adults without CV disease.[65,66] The effect of T deficiency on arterial stiffness appears to be more prominent in adult men (<60 years) and in subjects with higher blood pressure (mean pressure ≥ 102 mmHg).[65] T exerts a long-term influence on the arteries, as indicated by the findings of a longitudinal study that demonstrated that low serum T levels are an independent predictor of the arterial stiffness index.[62] Moreover, there is evidence that acute or chronic T treatment has a favorable effect on arterial stiffness in older men with T deficiency and coronary disease.[63,67]

TABLE 1 Summary of the effects of testosterone on vessel and endothelial function: small, medium, large vessels

Testosterone target	Molecular effect	Physiological effect
Coronary arteries vasomotion		
Large-conductance calcium-activated K channels[48-50]	Activation	Vasodilation
Voltage-sensitive K channels[50]	Activation	Vasodilation
ATP-sensitive K channels[51]	Activation	Vasodilation
L-type Ca channels[52-54]	Inactivation	Vasodilation
Store-operated Ca channels[55]	Inactivation	Vasodilation
Hydrogen sulfide[6]	Increased expression and activation of TRPV4 and large-conductance calcium-activated K channels	Vasodilation
Endothelial nitric oxide synthase (eNOS)[57,58]	Increased expression and activity and increased NO production	Vasodilation
Peripheral arterial stiffness		
Growth arrest-specific gene 6 (GAS6)[70]	Activation	Reduced apoptosis and calcification of vascular smooth muscle cells (VSMCs)
Growth arrest-specific gene 6 (GAS6)[71]	Activation with reduced expression and activity of matrix metalloproteinase-2 and collagen synthesis induced by angiotensin II	Reduced senescence of VSMCs
Large vessels atherosclerosis		
Tumor necrosis factor (TNF)-α[86,87]	Inhibition of TNF-α-induced vascular cell adhesion protein 1 (VCAM-1) expression	Reduced leukocyte adhesion to endothelium
TNF-α, interleukin (IL)-1β, IL-6, IL-10[89,90]	Reduced production of proinflammatory cytokines by antigen-presenting cells (APC), increased production of anti-inflammatory cytokines	Decreased inflammation
Lipopolysaccharide (LPS)[91]	Inhibition of LPS-induced VCAM-1 and intercellular adhesion molecule-1 (ICAM-1) expression	Reduced endothelial inflammatory response
Reactive oxygen species (ROS) – Vascular smooth muscle cells (VSMCs)[92,93]	Induction of ROS production from VSMCs	Promotion of ROS induced VSMCs migration and apoptosis
Prostate overexpressed protein 1 (PTOV1)[94]	Increased expression	Induction of VSMCs proliferation

Note: Coronary arteries vasomotion: Testosterone exerts a vasodilating action through a rapid, non-genomic, and endothelial-independent action on K and Ca channels. Moreover, it has also an endothelial-dependent vasodilating effect mediated by NO. *Peripheral arterial stiffness*: Testosterone reduces arterial stiffness through an androgen receptor-dependent modulation of apoptosis and senescence of vascular smooth muscle cells. Testosterone vasodilating action and anti-inflammatory effect may also have a role. *Large vessels atherosclerosis:* Testosterone exerts several anti-atherogenic actions, including an anti-inflammatory effect which may hinder the initial development of atheroma. The effect on VSMSs are complex and may be reliant on the stage of plaque development. VSMCs migration and proliferation could be considered protective against plaque destabilization, while VSMCs apoptosis could be responsible of plaque vulnerability.

The mechanisms by which T affects arterial stiffness are poorly understood. Several mechanisms have been proposed, including the vasodilating action of T[47,65] as well as the modulating action of T on the apoptosis and proliferation of vascular smooth muscle cells[47,65] and its anti-inflammatory effects.[47,65] Growth arrest-specific 6 (GAS6) gene is an important pro-survival agent that functions by decreasing the apoptosis of vascular smooth muscle cells via the PI3K/Akt pathway[68] as well as by reducing their inorganic phosphate (Pi)-induced calcification.[69] T regulates GAS6 transactivation via an AR-dependent mechanism.[70] Moreover, T-mediated GAS6 activation can regulate vascular smooth muscle cell senescence. T can restore angiotensin II (Ang II)-induced downregulation of GAS6 in vascular smooth muscle cells, resulting in the reduced expression and activity of matrix metalloproteinase-2 (MMP-2) and collagen synthesis induced by Ang II (Table 1).[71]

2.3 | Large vessel atherosclerosis

Several studies have demonstrated that low T levels are independently associated with carotid intimal-media thickness (CIMT),[72-75] a surrogate marker of atherosclerosis that predicts CV events.[76,77] Lower levels of T are also associated with accelerated progression of CIMT.[73] The effects of TRT have been evaluated in a randomized placebo-controlled study. This study showed that T treatment (T undecanoate, 1000 mg every 12 weeks) resulted in a significant reduction in CIMT in men with metabolic syndrome and LOH, which was found to be related to the increase in plasma T levels from baseline.[78] More recently, the long-term effects of T administration (T gel 1%; starting dose, 7.5 g daily) on CIMT or the coronary artery calcium score have been studied in older men with low or low-normal T levels. The results of this randomized placebo-controlled trial showed no significant difference in the rate of change of either CIMT or the coronary artery calcium score. A possible confounding factor that might explain these negative results may be the use of statins. Indeed, in exploratory analyses that have only included statin non-users, the annual rate of change of coronary artery calcium score was lower in the T group than in the placebo group; on the other hand, in statin users, no differences were observed between the two groups.[79] In another trial, the effect of T on coronary artery plaque volume was studied in symptomatic hypogonadal men aged > 65 years. Compared with placebo, T treatment (T gel 1%; starting dose, 5 g daily) was associated with a significant increase in non-calcified plaque volume and total plaque volume without any significant change in coronary calcium score. Moreover, an exploratory analysis showed that T therapy significantly increased fibrous plaque volume compared with placebo.[80] Therefore, T could promote a more stable plaque with a lower risk of rupture.[81] Clearly, metabolic impairment is a major modulator of CV risk, particularly of atherosclerotic risk, in males with hypogonadism. A detailed review of the changes in metabolic status under T replacement has been recently published.[16]

The exact mechanism by which T mediates its effects on atherogenesis remains unclear; however, several pathways have been explored. In mouse models, T replacement was shown to inhibit fatty streak formation.[82] The attachment of leukocytes to endothelial surfaces is a key step in the initial development of atheroma, and this process is facilitated by the enhanced expression of vascular cell adhesion protein 1 (VCAM1).[83-85] Tumor necrosis factor (TNF)-induced expression of VCAM1 can be suppressed by T in human aortic endothelial cells[86] and human umbilical vein endothelial cells.[87] Furthermore, this study has reported that the aromatization of T to estradiol is important in this protective T effect.[87] However, another study has reported divergent results.[88]

Another potential mechanism is the anti-inflammatory effect of T. Indeed, T suppresses serum proinflammatory cytokines, such as TNF-α and interleukin (IL)-1β, and promotes anti-inflammatory actions mediated by IL-10.[89] Moreover, T can inhibit the release of TNF-α, IL-1β, and IL-6 from the cultured monocytes of T-deficient men with type 2 diabetes,[90] furthermore T reduces lipopolysaccharide (LPS)- and TNFα-induced inflammatory response in endothelial cells.[91]

T exerts multiple AR-dependent and AR-independent actions on vascular smooth muscle cells, including the induction of reactive oxygen species (ROS),[92,93] extrinsic apoptosis,[93] migration,[92] and proliferation.[94] Therefore, the consequences of the actions of T on vascular smooth muscle cells in patients with atherosclerosis are difficult to elucidate and may rely on the stage of plaque development (Table 1).[47]

2.4 | Primary hemostasis

It has been reported that T might have prothrombotic effects in androgenic steroids users[95] and could lead to an increased risk of myocardial infarction and stroke.[96] Accordingly, current EAA guidelines suggest that TRT should not be initiated in patients with a recent major acute CV event.[33] Indeed, T enhances thromboxane A2 (TXA2) receptor density in human platelets, thereby increasing ex vivo platelet aggregability.[97] These data have been confirmed in a study conducted in castrated older men showing a lower maximum platelet aggregation response.[98] However, contrasting results have been shown in subsequent animal studies.[99-102] In castrated rats, the restoration of the physiological doses of androgens inhibited oxidative stress-induced platelet aggregation and reduced TXA2 release from platelets.[100] Moreover, T could inhibit platelet aggregation via increased NO synthesis, which is associated with endothelial cell growth.[101] Similar results were also obtained in a study that included men aged 60-65 years. This study showed that low levels of T and dihydrotestosterone (DHT) were significantly related to platelet activation and reactivity.[103] Moreover, an in vitro model has confirmed that both T and DHT significantly inhibit platelet aggregation triggered by arachidonate or collagen.[103] However, a recent study failed to show any difference in the procoagulant state of treated or untreated men with Klinefelter syndrome (KS) but demonstrated that thrombin generation

in men with KS was inversely associated with androgen action and that it was lower in treated subjects than in untreated subjects.[104] Finally, the largest available meta-analysis revealed no risk of venous thromboembolism (VTE) associated with TRT.[105] Because the risk of VTE could be higher in the presence of thrombophilia,[33] EAA guidelines suggest obtaining a detailed personal and family history of VTE and related risk factors before starting TRT.[33]

Overall, the currently available data suggest that the effects of T on primary hemostasis are complex and not yet fully understood; however, if any risk exists, it appears to be very low under physiological replacement (Table 2).

2.5 | Cardiac contractility and remodeling

Clinical data suggest that T has an influence on cardiac contractility. The effect of acute T administration has been evaluated in a randomized placebo-controlled trial in men with moderate-to-severe left ventricular dysfunction. A single dose of buccal T (60 mg) increased cardiac output and reduced systemic vascular resistance, with the maximal effect observed at 180 minutes. The main contributor to the improvement in left ventricular function could be the decrease in peripheral vascular resistance as suggested by the absence of an acute improvement in pulmonary wedge pressure.[106] Furthermore, T therapy (combined T esters, 100 mg every 2 weeks) has been shown to improve exercise capacity and symptoms in men with moderate heart failure (ventricular ejection fraction, 35%).[107] Subsequently, three randomized placebo-controlled trials confirmed the beneficial effects of T administration on functional exercise capacity and symptoms.[108-110] The increase in serum T level was directly related to the benefits on functional exercise capacity,[108] which may instead be related to improved overall skeletal muscle strength.[108,109] Moreover, a significant increase in left ventricular length (T patch, 5 mg daily) and a significant improvement in New York Heart Association class score were observed with T treatment.[108] It is noteworthy that only low doses of T have been used in the abovementioned randomized controlled trials because high doses can cause myocardial stiffening and hypertrophy.[111]

The effects of T on cardiac contractility and relaxation have also been demonstrated in preclinical studies. In isolated rat ventricular cardiomyocytes, exposure to T increased the rate of cardiomyocyte relaxation.[112] Moreover, in cardiomyocytes isolated from castrated rats, the maximum cardiomyocyte shortening was significantly

TABLE 2 Summary of testosterone molecular mechanisms and effects on primary hemostasis, oxygen delivery, salt retention, and muscle strength

Testosterone target	Molecular effect	Physiological effect
Primary hemostasis		
Thromboxane A2 (TXA2) receptor[97]	Increased density on platelets	Increased platelet aggregability
TXA2[100]	Reduced release from platelets	Reduced platelet aggregability
Endothelial nitric oxide synthase (eNOS)[101]	Increased expression and activity and increased NO production	Reduced platelet aggregability
Oxygen delivery		
Erythropoietin (EPO)[150]	Increased production	Increased erythropoiesis
Hepcidin[152]	Reduced expression	Increased iron incorporation into red blood cells
Salt retention and muscle strength		
Type II and type I muscle fiber[172]	Shift from type II to type I muscle fiber	Increased muscle strength
Angiotensinogen[173,174]	Increased expression	Increased salt and water retention
Na/H exchanger[74,175]	Increased expression and activity	Increased salt and water retention
Aquaporin 1[176]	Increased expression and activity	Increased salt and water retention
Epithelial sodium channel (ENaC)[177]	Increased expression and activity	Increased salt and water retention

Note: Primary hemostasis: Testosterone effects on primary hemostasis are complex. TXA2 and its receptor, which stimulate platelets activation and increase platelet aggregation, seem to mediate testosterone action in primary hemostasis. *Oxygen delivery*: Testosterone promotes erythropoiesis through a stimulation of EPO production, which is the major erythropoiesis-stimulating hormone, and increasing iron incorporation into red blood cells. *Salt retention and muscle strength*: Testosterone reduces fatigue related to chronic heart failure increasing muscle strength. However, testosterone could exacerbate chronic heart failure increasing salt and water retention.

TABLE 3 Summary of testosterone molecular mechanisms and effects on cardiac tissue

Testosterone target	Molecular effect	Physiological effect
Cardiac contractility and remodeling		
α1- and β1-adrenoceptors[114]	Increased activity	Increased ventricular contractility and relengthening
L-type calcium channel[115]	Increased expression	Increased ventricular contractility
Na/Ca exchanger[115]	Increased expression	Increased ventricular relengthening
Sarcoplasmic/endoplasmic reticulum calcium ATPase[114,116]	Increased activity	Increased ventricular relengthening
Angiotensin II and angiotensin type Ia receptor[117]	Increased expression	Increased maladaptive remodeling
Interleukin (IL)-10 and Tumor necrosis factor (TNF)-α[118]	Increased IL-10 and reduced TNF-α	Reduced inflammation
Mitochondria transcription factor A (Tfam)[119]	Increased expression	Reduced apoptosis
Serine-threonine kinase (Akt)[119]	Decreased phosphorylation	Reduced apoptosis
Angiotensin II receptor[120]	Reduced transcription	Reduced cardiac fibrosis
Bcl 2[120]	Reduced expression	Reduced apoptosis
Heat shock protein 70[122]	Increased expression	Delayed cardioprotection of ischemic preconditioning
Mitochondrial ATP-sensitive potassium channels[123]	Activation	Increased myocardial tolerance to ischemia
Cardiac electrophysiology		
Delayed-rectifier potassium channels (IKs)[137]	Activation	Facilitated ventricular repolarization
L-type calcium channels (ICaL)[137]	Inhibition	Facilitated ventricular repolarization
Delayed-rectifier potassium channels (IKr)[138]	Activation	Facilitated ventricular repolarization
Ultra-rapid potassium channels (IKur)[139]	Activation	Facilitated ventricular repolarization

Note: Cardiac contractility and remodeling: Testosterone seems to have an overall favorable effect on ventricular contractility and remodeling, with a protective effect on cardiomyocytes. *Cardiac electrophysiology*: Testosterone also promotes ventricular repolarization through a direct action on several ion channels involved in the generation of the action potential.

reduced and relaxation was delayed compared with controls or T-treated orchiectomized rats.[113] Physiological levels of T increase positive inotropic response and myocardial relaxation to α1-adrenergic and β1-adrenergic receptors stimulation via an AR-dependent action.[114] Other mechanisms by which T can modulate cardiac performance are by regulating the functional expression of the L-type calcium channel and Na/Ca exchanger,[115] increasing calcium release via the ryanodine receptor, and enhancing calcium clearance by increasing sarcoplasmic/endoplasmic reticulum calcium ATPase levels.[114,116]

In animal studies, T has been shown to induce the activation of the renin-angiotensin-aldosterone system (RAAS), resulting in increased maladaptive remodeling.[117] In contrast, it has been shown that T treatment can suppress ventricular remodeling and improve cardiac function in rats, diminishing the imbalance between IL-10 and TNF-α.[118] In addition, it has been demonstrated that T, via the AR system, exerts a protective action against angiotensin II-induced cardiac remodeling.[119,120]

There is evidence that T has a beneficial effect on myocyte survival. Indeed, the immediate cardioprotection of ischemic preconditioning is lacking in the absence of T.[121] Moreover, T mediates delayed cardioprotection by inducing heat shock protein 70 (HSP-70),[122] while the induction of ATP-sensitive potassium channels in the mitochondrial inner membrane by T could represent another mechanism of myocyte protection (Table 3).[123]

2.6 | Cardiac electrophysiology

Growing evidence suggests that T has a direct effect on the cardiac conduction system, particularly on ventricular repolarization.[124]

The role of T is corroborated by the evidence that after puberty, the corrected QT (QTc) interval is significantly shorter in boys than in girls.[125] Subsequent studies have found a negative correlation between endogenous serum T levels in adults and the QTc interval,[126] which is prolonged in hypogonadal men.[127,128] Accordingly, men with an early repolarization ECG pattern (rapidly ascending ST-segment) showed higher endogenous serum T levels than those without this pattern.[129]

Moreover, the age-related decline in serum T levels could in part explain the age-dependent prolongation of the QTc interval in men.[130] Ventricular arrhythmias, such as torsade de pointes, and sudden cardiac death are associated with prolonged QTc intervals.[131-133] Indeed, as shown in a single-center case series of seven patients, male hypogonadism was associated with torsade de pointes, possibly representing a reversible cause of this life-threatening tachyarrhythmia, which could be treated or prevented by TRT.[134] Moreover, T treatment has been shown to shorten the QTc interval length in community-dwelling men[135] as well as in those with chronic heart failure (CHF).[136]

In animal models, T administration facilitated cardiomyocyte repolarization and shortened the action potential duration. T can increase the gradual activation of delayed-rectifier potassium currents (IKs),[137] inhibit inward depolarizing L-type calcium currents (ICaLs),[137] increase the rapid activation of delayed-rectifier potassium currents (IKr),[138] and increase ultra-rapid potassium currents (IKur).[139] However, chronic T treatment increased ICaLs via AR activation,[140] while the opposite was observed for acute T administration,[137] suggesting the existence of a complex network of modulation (Table 3).

2.7 | Oxygen delivery

The role of T in the regulation of erythropoiesis is well-known,[141,142] and increased hematocrit is the most frequent adverse effect of TRT in men with hypogonadism men.[14] The stimulatory effect of T on erythropoiesis is dose-dependent and is more pronounced in older men.[143] In a recent randomized placebo-controlled trial that included older men with T deficiency, T therapy significantly increased the hemoglobin levels of all anemic patients, including those with unexplained anemia, as well as those who were not anemic.[144] Therefore, given that T treatment can improve unexplained anemia in older men, the evaluation of T levels should be considered in men who have unexplained anemia as well as symptoms suggestive of T deficiency.[144] Furthermore, T therapy could have beneficial effects in men with chronic anemia and CHF. Indeed, an increase in hematocrit may improve the symptoms of CHF.[108] In fact, the oxygen-transporting capacity is improved by an increased number of erythrocytes within a physiologic range.[145] Favorable effects of TRT have also been observed in men with chronic kidney disease (CKD)[146] in whom hypogonadism may be an additional cause of anemia with reduced responsiveness of erythropoiesis-stimulating agents.[147] However, as shown in animal studies, blood viscosity is increased by T-induced erythropoiesis,[148] leading to an increase in blood flow resistance. Moreover, a correlation between hematocrit and platelet aggregation has been demonstrated, suggesting that an increased number of erythrocytes could increase the risk of thrombosis.[149] Therefore, EAA guidelines do not recommend TRT in the presence of elevated hematocrit.[33]

T stimulates erythropoiesis, increasing erythropoietin (EPO) levels and iron utilization.[150] EPO secretion could be stimulated by T by inducing hypoxia or hypoxic sensing.[151] Furthermore, it could regulate the expression of hypoxia-inducible factors (HIFs), Von Hippel-Lindau (VHL), prolyl hydroxylase (PHD), or EPO.[150-152] Alternatively, T could affect renal physiology by altering EPO secretion from erythropoietin-producing cells.[153] Increased iron utilization is suggested by the reduction of ferritin and hepcidin concentrations induced by T.[150] Indeed, T can regulate hepcidin expression by regulating bone morphogenetic protein (BMP) signaling pathways (Table 2).[152]

2.8 | Chronic heart failure

Among men with CHF, approximately one-third show T deficiency.[154] Moreover, in men with CHF, low T levels independently correlate with exercise intolerance[155] and are associated with muscle wasting and cachexia.[156,157] Therefore, it has been postulated that T deficiency is involved in the pathophysiology of CHF, contributing to some extent to its clinical features, such as fatigue and dyspnea.[158,159] It has also been shown that low T levels are related to poor prognosis, increased hospital admissions, and all-cause mortality in men with CHF.[160,161] This evidence suggests that T treatment may ameliorate the clinical status of hypogonadal patients with CHF by improving muscle strength and functional pulmonary capacity.[162] However, some of the adverse CV events reported in the TOM trial were related to an exacerbation of CHF.[29] Indeed, T modulates salt and water homeostasis by promoting salt and water retention as well as the expansion of the extracellular water volume.[163] A 2012 meta-analysis of randomized controlled trials strengthened the evidence of a beneficial effect of T treatment on exercise capacity and oxygen consumption in patients with CHF.[164] However, a more recent meta-analysis showed that TRT did not improve the exercise capacity, cardiac function, quality of life, or clinical outcome of patients with CHF.[165] Taken together, current EAA guidelines recommend against the use of TRT in patients with severe CHF given the risk of polycythemia and VTE in a frail population.[33]

Impaired skeletal muscle function and muscle atrophy are features of CHF that could be related to the state of chronic inflammation and insulin resistance characterizing these patients.[166,167] Inflammation has been demonstrated to be promoted by TNF-α, IL-1β, and IL-6.[167] Although the anti-inflammatory action of T is well-known,[89] treatment with a T patch for 3 months (5 mg daily) in men with CHF did not show a reduction in TNF-α levels.[168] The insulin resistance of these patients, which is related to worse symptomatic status,[169] could be linked to a

decrease in the glucose transporter GLUT4.[166] There is evidence that T treatment improves insulin sensitivity[109,170,171] and reduces fasting glucose levels[170] in men with CHF and metabolic syndrome or type 2 diabetes. Another mechanism that could have a role in the improved exercise capacity and muscle strength promoted by T in these patients is the shift from type II to type I muscle fiber.[172] Salt and water retention promoted by T are mediated by the proximal tubule RAA system by the increased expression of angiotensinogen[173,174] and increased expression and activity of Na/H exchanger[174,175] and aquaporin 1[176] in the proximal tubules and the epithelial sodium channel in the collecting ducts (Table 2).[177]

3 | CONCLUSIONS

Using the reductio ad absurdum logic, we contradicted the initial assumption of an overall harmful effect of T on the CV system. Although T has been demonstrated to have overall favorable effects on vasomotion, arterial stiffness, atherosclerosis, cardiac electrophysiology, oxygen delivery, cardiac contractility, and remodeling, it possesses a prothrombotic effect due to its action on platelet function and blood viscosity. In summary, based on the current evidence, CV disease does not appear to be increased in patients undergoing TRT.[178,179] Most physicians against TRT will argue that TRT is "neutral" in terms of CV safety. While the latter is possible, the indication for TRT has never been to address CV dysfunction but rather to improve various signs and symptoms in LOH that correlate well with low testosterone levels. Nonetheless, in older patients with a known CV risk factor, a tailored approach is suggested.[14,25] Symptoms, comorbidities, baseline and target levels of T, formulation, and therapy timing[25,180,181] should be considered to improve sexual function, mood, depressive symptoms, and the mobility of patients with low testosterone levels.[13,33,182,183]

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR'S CONTRIBUTIONS

FS, DG, and AMI designed the study concept. FS, MM, RP, and MT performed data analysis and interpretation. All authors drafted the manuscript for important intellectual content.

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