Přehledový článek | Review article

Testosterone Replacement Therapy and Cardiovascular Safety: A Paradigm Shift in Cardiological Practice

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SOUHRN

Úvod: Hypogonadismus je častým, avšak často přehlíženým stavem u mužů s diabetem 2. typu, obezitou a kardiovaskulárním onemocněním. Nízké koncentrace testosteronu jsou spojeny s nepříznivým kardiometabolickým profilem a zvýšenou mortalitou. Testosteronová substituční terapie (TRT) byla však po dlouhou dobu vnímána s obavami z možného zvýšení kardiovaskulárního rizika, a to především na základě observačních studií s významnými metodologickými omezeními.
Cíl: Cílem tohoto přehledového článku je shrnout současné poznatky o vztahu testosteronu, hypogonadismu a kardiovaskulárního rizika, objasnit patofyziologické mechanismy působení testosteronu na kardiovaskulární systém a diskutovat klinický význam recentních důkazů o bezpečnosti testosteronové substituce, se zvláštním důrazem na studii TRAVERSE.
Metody: Byla provedena analýza dostupných observačních studií, metaanalýz a randomizovaných klinických studií hodnotících vztah hypogonadismu, testosteronové substituční terapie a kardiovaskulárních příhod se zaměřením na studii TRAVERSE jako dosud největší randomizovanou studii hodnotící kardiovaskulární bezpečnost TRT.
Výsledky: Hypogonadismus je vysoce prevalentní u mužů s diabetem 2. typu a obezitou a podílí se na rozvoji inzulinové rezistence, endoteliální dysfunkce, aterogenního lipidového profilu a chronického zánětu. Dřívější obavy z kardiovaskulárního rizika TRT vycházely převážně z observačních studií s významnými metodologickými limity. Randomizovaná studie TRAVERSE prokázala, že testosteronová substituční terapie u mužů s hypogonadismem a vysokým kardiovaskulárním rizikem nebyla spojena se zvýšeným výskytem závažných kardiovaskulárních příhod.
Závěr: Studie TRAVERSE poskytuje dosud nejpřesvědčivější důkaz o kardiovaskulární bezpečnosti testosteronové substituční terapie při správné indikaci a monitoraci. Hypogonadismus by měl být vnímán jako klinicky významný kardiometabolický rizikový faktor, nikoli pouze jako okrajový endokrinologický problém. Testosteronová substituce může být bezpečně zvažována i u pacientů se stabilním kardiovaskulárním onemocněním, avšak vyžaduje individualizovaný přístup a mezioborovou spolupráci.

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ABSTRACT

Background: Hypogonadism is a common but frequently underdiagnosed condition in men with type 2 diabetes, obesity, and cardiovascular disease. Low testosterone levels are associated with an adverse cardiometabolic profile and increased mortality. However, testosterone replacement therapy (TRT) has long been considered potentially harmful with respect to cardiovascular risk, largely based on observational studies with significant methodological limitations.
Aim: To summarize current evidence on the relationship between testosterone, hypogonadism, and cardiovascular risk, to describe the pathophysiological mechanisms linking testosterone deficiency to cardiovascular disease, and to discuss the clinical implications of recent evidence on the cardiovascular safety of testosterone replacement therapy, with particular emphasis on the TRAVERSE trial.
Methods: A narrative review of observational studies, meta-analyses, and randomized controlled trials evaluating hypogonadism, testosterone replacement therapy, and cardiovascular outcomes was performed, with a focus on the TRAVERSE trial as the largest randomized study specifically designed to assess the cardiovascular safety of TRT.

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Results: Hypogonadism is highly prevalent in men with type 2 diabetes and obesity and contributes to insulin resistance, endothelial dysfunction, an atherogenic lipid profile, and chronic inflammation. Earlier concerns regarding cardiovascular risk associated with TRT were mainly derived from observational studies with substantial methodological limitations. The randomized TRAVERSE trial demonstrated that testosterone replacement therapy in men with hypogonadism and high cardiovascular risk was not associated with an increased incidence of major adverse cardiovascular events.
Conclusion: The TRAVERSE trial provides the most robust evidence to date supporting the cardiovascular safety of testosterone replacement therapy when appropriately indicated and monitored. Hypogonadism should be regarded as a clinically relevant cardiometabolic risk factor rather than a marginal endocrine condition. Testosterone replacement therapy may be safely considered in men with stable cardiovascular disease, emphasizing the need for individualized decision-making and interdisciplinary collaboration.

Introduction

Testosterone has traditionally been viewed primarily as a hormone responsible for male sexual function and reproductive health. However, this perspective does not reflect the current understanding of its complex biological effects. Testosterone plays a significant role in regulating energy metabolism, body composition, insulin sensitivity, inflammatory pathways, and the function of the cardiovascular system. Low testosterone levels have been associated with an increased incidence of obesity, type 2 diabetes (T2DM), metabolic syndrome, and atherosclerotic cardiovascular diseases.[1]

Hypogonadism, defined by a combination of low testosterone levels and the presence of clinical symptoms, is a common but often unrecognized condition in men with high cardiometabolic risk. Numerous observational studies have demonstrated that low testosterone concentrations are associated with increased overall and cardiovascular mortality, independent of age and traditional risk factors.[2] Nevertheless, testosterone replacement therapy (TRT) was for a long time approached with caution, especially within the cardiology community, primarily due to concerns about a potential increase in cardiovascular risk. These concerns stemmed from several observational studies published in the first half of the previous decade, which suggested a possible association between TRT and a higher incidence of major cardiovascular events.[3,4] As a result, there was significant therapeutic inertia and reluctance to indicate TRT in patients with existing cardiovascular disease or a high risk of its development. However, in recent years, there has been a substantial shift in understanding, thanks to new, methodologically robust clinical studies that allow for a more objective assessment of the cardiovascular safety of TRT.[5,6]

The aim of this review article is to summarize current evidence on the relationship between testosterone, hypogonadism, and cardiovascular risk, to clarify the pathophysiological mechanisms by which testosterone affects the cardiovascular system, and to critically evaluate the available data on the safety of testosterone replacement therapy, with particular emphasis on the recent randomized TRAVERSE trial, which represents a significant milestone in this field.

Prevalence of hypogonadism in patients with type 2 diabetes and obesity

Hypogonadism occurs significantly more often in men with type 2 diabetes and obesity than in the general population. Studies have confirmed that hypogonadism affects approximately 30–50% of men with T2DM, with prevalence increasing alongside greater insulin resistance and visceral obesity.[7–9]

Obesity, especially central obesity, plays a key role in the pathogenesis of hypogonadism. Increased aromatase activity in adipose tissue leads to higher conversion of testosterone to estradiol, which subsequently suppresses the hypothalamic–pituitary–gonadal axis. At the same time, insulin resistance, chronic subclinical inflammation, and altered gonadotropin secretion develop. This condition is often referred to as functional hypogonadism and is typical for patients with metabolic syndrome, T2DM, and cardiovascular disease.[10]

From a clinical perspective, the high prevalence of low testosterone in men with prediabetes is also significant. Men with impaired glucose tolerance or elevated fasting glucose have significantly lower total testosterone levels compared to normoglycemic individuals, even after adjusting for age and body weight. Thus, prediabetes represents a period during which hypogonadism and cardiometabolic risk mutually reinforce each other.[11]

Based on these findings, in 2018 the American Diabetes Association included recommendations to measure testosterone levels in men with diabetes and clinical symptoms of hypogonadism.[12] This fact underscores the growing importance of hypogonadism not only as an endocrinological issue but also as a cardiometabolic problem that should be considered in cardiology practice as well.

Understanding primary, secondary, and functional hypogonadism in clinical practice

From a clinical and pathophysiological standpoint, hypogonadism is a heterogeneous condition that can be divided into three basic categories: primary, secondary, and functional hypogonadism.

Primary (hypergonadotropic) hypogonadism is characterized by primary testicular failure, in which testosterone production decreases despite elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Typical causes include genetic syndromes, testicular

damage due to infection, radiotherapy or chemotherapy, and advanced age.[13]

Secondary (hypogonadotropic) hypogonadism arises from regulatory disorders at the level of the hypothalamus or pituitary gland. It is characterized by low or inappropriately normal levels of gonadotropins in the presence of low testosterone. This type of hypogonadism may occur with structural lesions of the central nervous system, hyperprolactinemia, or in connection with chronic systemic diseases.[13]

In addition to these classic forms, clinical practice is increasingly encountering so-called **functional hypogonadism**, which has a different pathophysiology and clinical consequences. Functional hypogonadism, often referred to as late-onset hypogonadism (LOH), is a potentially reversible condition closely associated with obesity, insulin resistance, chronic subclinical inflammation, and metabolic syndrome. Unlike primary and secondary hypogonadism, there is no structural disorder of the hypothalamic–pituitary–gonadal axis. Functional hypogonadism represents the most common form of low testosterone in men with type 2 diabetes and cardiovascular disease and is also a key link between hypogonadism and increased cardiovascular risk.[1,14]

Metabolic effects of testosterone and insulin resistance

One of the key mechanisms linking hypogonadism to cardiovascular risk is insulin resistance. Testosterone plays a crucial role in body fat distribution and the maintenance of muscle mass. Low levels of testosterone are associated with an increase in visceral adipose tissue, which is metabolically active and produces a range of pro-inflammatory mediators that promote insulin resistance.[15,16]

At the cellular level, testosterone increases the expression of the insulin receptor, insulin receptor substrate (IRS-1), and glucose transporter GLUT4 in muscle tissue, thereby improving insulin-dependent glucose uptake. Conversely, testosterone deficiency is associated with reduced muscle mass and a relative increase in fat mass, which further worsens insulin sensitivity and contributes to the development of hyperglycaemia.[17]

Testosterone, lipid metabolism, and atherogenic profile

Testosterone affects lipid metabolism through both direct and indirect mechanisms. Low levels of testosterone are associated with an atherogenic lipid profile characterized by elevated triglycerides, non-HDL cholesterol, and an unfavorable triglyceride/HDL ratio, which is considered a marker of insulin resistance and cardiovascular risk. An important aspect is the fact that testosterone influences not only individual lipid fractions but the entire spectrum of atherogenic lipoproteins. Non-HDL cholesterol, which includes all apoB-containing lipoproteins, is considered a better predictor of cardiovascular risk than LDL cholesterol alone, especially in patients with diabetes and hypertriglyceridemia. Hypogonadism is associated with increased levels of non-HDL cholesterol and remnant lipoproteins, which further promote atherogenesis.[18]

Vascular effects of testosterone and endothelial function

Testosterone has direct effects on the arterial wall. Both experimental and clinical studies have shown that testosterone acts as a vasodilator, primarily by stimulating the synthesis of nitric oxide (NO) in the endothelium and through a direct relaxing effect on vascular smooth muscle.[19,20] Low testosterone levels are associated with endothelial dysfunction, increased arterial stiffness, and impaired coronary vasodilation.[21,22] Endothelial dysfunction represents an early step in the development of atherosclerosis and is an independent predictor of cardiovascular events. Thus, hypogonadism may indirectly contribute to the progression of the atherosclerotic process even in its early stages.

Inflammation, immune response, and atherogenesis

Chronic low-grade inflammation is a key pathophysiological mechanism linking obesity, insulin resistance, and atherosclerosis. Hypogonadism is associated with elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6), as well as higher C-reactive protein (CRP) concentrations.[23]

In contrast, testosterone predominantly exerts immunomodulatory and anti-inflammatory effects. Testosterone replacement therapy has been associated in several studies with reduced levels of inflammatory markers and an improved inflammatory profile in patients with hypogonadism. These changes may contribute to slowing the progression of atherosclerosis and stabilizing atherosclerotic plaques.[23]

Electrophysiology and arrhythmogenesis

Testosterone influences ventricular repolarization. Hypogonadism is associated with a prolonged QTc interval, which is a known risk factor for Torsades de Pointes (TdP) and sudden cardiac death. It has been demonstrated that testosterone replacement therapy (TRT) shortens the QTc interval, suggesting a protective effect against ventricular arrhythmias through modulation of hERG potassium channels.[24–26]

Hematopoiesis and coagulation

The most common adverse effect of testosterone replacement therapy (TRT) is erythrocytosis. Testosterone stimulates the production of erythropoietin (EPO) and suppresses hepcidin, which increases iron utilization and the formation of red blood cells. Elevated hematocrit increases blood viscosity, which theoretically raises the risk of stasis and thrombosis. This is the main mechanism by

which the potential risk of venous thromboembolism (VTE) is explained.[27] In addition, testosterone has been reported to reduce platelet aggregation and the density of thromboxane A2 receptors, which could theoretically compensate for the risk of increased viscosity.[28]

The main systemic changes in untreated hypogonadism and after TRT, along with their cardiological implications, are summarized in **Table 1**.

Controversies surrounding testosterone replacement therapy and cardiovascular risk

Despite the growing evidence of the unfavorable cardiometabolic profile associated with hypogonadism, testosterone replacement therapy (TRT) was, for a long time, considered potentially risky in terms of cardiovascular safety. These concerns significantly influenced clinical practice, particularly in the field of cardiology, leading to caution or outright rejection of TRT for patients with existing cardiovascular disease.

A major turning point in the perception of TRT came after the publication of several observational studies in 2013–2014. The most frequently cited work is a retrospective analysis published by Vigen et al.,[3] which reported a higher incidence of a composite cardiovascular endpoint in men with low testosterone who had undergone coronary angiography and were treated with testosterone, compared to those untreated. Shortly thereafter, Finkle et al.[4] published a database-based analysis suggesting an increased risk of non-fatal myocardial infarction after initiating TRT, particularly in older men and in patients with pre-existing cardiovascular disease.

These studies attracted media and professional attention and led to regulatory actions, including warnings from the U.S. FDA (Food and Drug Administration) regarding the potential cardiovascular safety of testosterone products.[29] However, it is important to emphasize that both studies had significant methodological limitations that significantly constrain the interpretation of their findings. In contrast to the FDA, the EMA (European Medicines Agency) adopted a more cautious approach. After reviewing the available evidence, it stated that the data on increased cardiovascular risk are inconsistent, and the interpretation of these studies is therefore not definitive.[30]

The retrospective observational design represents the main weakness of most studies that highlighted a possible increase in cardiovascular risk associated with TRT. These works lacked randomization, testosterone treatment was not standardized, and the precise definition of hypogonadism was often missing. In many cases, it was unclear whether patients achieved physiological testosterone levels, or what their adherence to treatment was.

Another major issue was patient selection. The observed cohorts often included men with very high cardiovascular risk, polymorbid patients, and individuals shortly after acute cardiovascular events. These factors alone substantially increase the risk of cardiovascular events and can lead to so-called "confounding by indication", where treatment is prescribed to patients with poorer overall health status.

In addition, analytical errors were subsequently identified in some studies. In the case of the work by Vigen et al., the original results were subsequently corrected, with data reanalysis leading to a change in the direction of some conclusions. These circumstances further undermined the robustness of the initial claims about the increased cardiovascular risk of TRT.

In the following years, a number of meta-analyses were published that attempted to summarize the available data on the cardiovascular safety of testosterone replacement therapy. The results of these studies were heterogeneous and often depended on the included trials, duration of follow-up, and the definition of the assessed endpoints.[31–33] However, a common feature of most of these analyses was the absence of long-term randomized

Table 1 – Overview of the main systemic changes in untreated hypogonadism and after testosterone replacement therapy (TRT) and their possible cardiological implications

Parameter	Untreated hypogonadism (deficiency)	After testosterone replacement therapy (TRT)	Cardiology implications of TRT
Glucose metabolism[15–17]	Insulin resistance, high risk of progression to type 2 diabetes, higher HbA_{1c}	Increased insulin sensitivity, reduction in HbA_{1c}, potential remission of prediabetes	Reduced glucotoxicity and lower risk of microvascular complications
Body composition[16]	Accumulation of visceral fat, sarcopenia (loss of muscle mass), reduced basal metabolic rate	Reduction in fat mass (especially visceral), increase in lean (muscle) mass	Improved metabolic profile, reduced joint load, increased physical fitness
Inflammation[23]	Elevated pro-inflammatory cytokines (TNFα, IL-6, CRP); chronic low-grade inflammation	Suppression of pro-inflammatory cytokines; reduction of systemic inflammation	Atherosclerotic plaque stabilization; reduced endothelial dysfunction
Hematopoiesis[27,28]	Frequent mild anemia (normocytic, normochromic); reduced oxygen-carrying capacity	Stimulation of erythropoiesis; increased hemoglobin and hematocrit	Improved tissue oxygenation (potential benefit in heart failure), but risk of hyperviscosity with overtreatment
Mental health and vitality[1]	Fatigue, reduced motivation, depression, lethargy ("metabolic fatigue")	Improvement in mood, energy, motivation, and libido	Better adherence to lifestyle measures (exercise, diet)

studies with sufficient statistical power to allow a definitive conclusion.

The ambiguous data led to significant caution in clinical practice regarding the indication of TRT, especially in patients with cardiovascular disease or those at high risk of developing it. This approach was understandable in the context of the "primum non nocere" principle; however, it may also have resulted in undertreatment of symptomatic patients with hypogonadism and in overlooking its potential impact on cardiometabolic health.

The lack of prospective randomized trials primarily designed to assess the cardiovascular safety of testosterone replacement therapy represented a major gap in the available evidence. This gap was filled only recently by the TRAVERSE study, which was specifically designed to assess the cardiovascular risks of TRT in men with hypogonadism and high cardiovascular risk.[34]

TRAVERSE Study

A major breakthrough in the assessment of the cardiovascular safety of testosterone replacement therapy was brought by the randomized, placebo-controlled TRAVERSE trial (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men), published in 2023.[6] The study was specifically designed to evaluate the relationship between TRT and the incidence of major adverse cardiovascular events in men with hypogonadism and concomitantly increased cardiovascular risk – precisely the population that has been the subject of the greatest concerns and controversies in clinical practice.

Study design and population characteristics

TRAVERSE was a multicenter, randomized, double-blind, placebo-controlled non-inferiority trial. The study enrolled 5,246 men aged 45–80 years with clinically and laboratory-confirmed hypogonadism, defined by two morning total testosterone levels below 300 ng/dl (≈10.4 nmol/l) and the presence of typical symptoms. The average BMI was 35 kg/m²; 70% had type 2 diabetes mellitus, and 90% had hypertension and dyslipidemia. Participants also had either established cardiovascular disease or were burdened with multiple cardiovascular risk factors.

Patients were randomized to daily application of transdermal 1.62% testosterone gel or placebo. The dose was titrated to maintain testosterone levels within the physiological range (350–750 ng/dl ≈ 12.1–26.0 nmol/l), which distinguishes this study from earlier works where supraphysiological peaks occurred, especially with injectable forms of therapy. The average duration of treatment was 21.7 months, and the mean follow-up period was 33 months.

Primary cardiovascular outcomes

The primary safety endpoint was the first occurrence of a major adverse cardiovascular event (MACE), defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The study clearly met the criteria for non-inferiority: the primary endpoint occurred in 7% of patients in the testosterone-treated group and 7.3% in the placebo group (hazard ratio 0.96; 95% CI 0.78–1.17; p <0.001 for non-inferiority). The results were consistent across each component of the primary endpoint and did not provide evidence of increased risk for cardiovascular mortality, myocardial infarction, or stroke. These data fundamentally refute concerns raised by earlier observational studies, especially the works by Vigen and Finkle.[3,4]

Following the publication of the TRAVERSE results, the FDA updated the labeling information for testosterone products and removed the boxed warning regarding increased cardiovascular risk.[35]

Secondary outcomes and safety signals

Secondary analyses provided clinically relevant details. Overall mortality and the need for coronary revascularization were comparable between the testosterone and placebo groups. On the other hand, a higher incidence of atrial fibrillation was observed in the testosterone-treated group (3.5% vs. 2.4%). There was also a slightly higher occurrence of acute kidney injury (2.3% vs. 1.5%) and pulmonary embolism (0.9% vs. 0.5%). Although the absolute differences were small, these findings highlight the necessity for careful monitoring, particularly of hematocrit and hydration, during testosterone therapy.[12]

The main cardiovascular outcomes and safety signals from the TRAVERSE study are summarized in **Table 2**.

Table 2 – TRAVERSE – overview of results and safety signals

Outcome	Testosterone vs. placebo	Hazard ratio (HR) / Result	Interpretation
All-cause mortality	Similar	0.96	TRT does not increase mortality.
Coronary revascularization	Similar	NS	No difference in the frequency of coronary revascularizations (PCI/CABG)
Atrial fibrillation (AFib)	3.5% vs. 2.4%	Increased risk	Higher incidence of atrial fibrillation; clinical vigilance recommended
Acute kidney injury (AKI)	2.3% vs. 1.5%	Increased risk	Statistically significant, but the absolute difference is small (<1%).
Pulmonary embolism (PE)	0.9% vs. 0.5%	Increased risk	Likely related to erythrocytosis

CABG – coronary artery bypass graft; HR – hazard ratio; NS – not statistically significant; PCI – percutaneous coronary intervention; TRT – testosterone replacement therapy.

Efficacy and non-sexual benefits of treatment

The TRAVERSE trial also provided data on the efficacy of TRT in non-sexual domains. Testosterone therapy led to the correction of anemia in hypogonadal men, which may be clinically significant especially for patients with heart failure or coronary artery disease. Metabolic benefits were further confirmed in substudies and related works, including the T4DM study, which showed that long-term TRT can slow or prevent the progression from prediabetes to type 2 diabetes.[36]

Summary of the significance of the TRAVERSE trial

The TRAVERSE trial provides the highest-quality and most robust evidence to date supporting the cardiovascular safety of testosterone replacement therapy when appropriately indicated, dosed, and monitored. Its findings offer a solid foundation for rational, individualized decision-making on TRT in men with hypogonadism and high cardiovascular risk within a multidisciplinary care framework.

TRAVERSE study in the context of current meta-analyses and consensus evidence

The most recent synthesis of available data on the cardiovascular safety of testosterone replacement therapy is presented in an updated systematic review and meta-analysis of placebo-controlled randomized clinical trials published in 2024, which now includes the results of the TRAVERSE study and thus allows its conclusions to be assessed in the context of the entire spectrum of randomized evidence. Out of a total of 3,615 identified works, 106 studies were included in the analysis, encompassing 8,126 men treated with testosterone and 7,310 patients in the placebo group.[5]

When evaluating major adverse cardiovascular events (MACE), no differences were found between the testosterone-treated group and the placebo group. An increased incidence of nonfatal arrhythmias and atrial fibrillation was observed only in a single study,[6] which had cardiovascular safety as its primary endpoint; however, this finding was not confirmed when all other studies were included in the meta-analysis. Additionally, no association was found between endogenous testosterone levels and the occurrence of atrial fibrillation after adjustment for confounding factors. The authors therefore conclude that testosterone replacement therapy is not associated with an increased risk of major adverse cardiovascular events.

Clinical implications: management of a cardiology patient with suspected hypogonadism

Although there is currently no standalone Czech guideline specifically addressing routine testosterone screening in men with type 2 diabetes, clinical practice in the Czech Republic is aligned with European and U.S. recommendations, including guidance from the European Association of Urology (EAU), the European Society of Endocrinology (ESE), and the American Diabetes Association (ADA), and applies a pragmatic symptom-based case-finding approach.

From a practical perspective, cardiologists should consider hypogonadism particularly in men with type 2 diabetes, obesity, metabolic syndrome, or chronic cardiovascular disease who also report symptoms such as persistent fatigue, reduced exercise tolerance, loss of muscle strength, or impaired quality of life. Alternatively, the Aging Males' Symptoms (AMS) questionnaire may be used to screen for symptoms suggestive of hypogonadism. In these cases, an appropriate first step may be a screening of morning total testosterone levels, followed by referral to an endocrinology evaluation if low values are repeatedly found.

For cardiologists, it is particularly important to recognize that the presence of stable cardiovascular disease by itself does not represent a contraindication to testosterone replacement therapy, provided that the treatment is indicated based on clinical symptoms and laboratory-confirmed hypogonadism. The TRAVERSE study was conducted precisely in a population of men with high cardiovascular risk, and it did not demonstrate any increase in the incidence of major cardiovascular events with testosterone treatment.

If TRT is initiated in a patient with cardiovascular risk factors, it should be accompanied by a clear monitoring plan. The goal is to maintain testosterone within the physiological range while minimizing specific risks. A practical monitoring framework (frequency of follow-ups and action thresholds) is provided in **Table 3**.[15]

Table 3 – Monitoring patients on TRT: what to monitor and when to intervene

Parameter	Frequency	Target / Action threshold	Rationale
Hematocrit	Baseline, 3–6 months, then annually	Hold therapy / reduce dose if **>54%**	Minimize hyperviscosity and thromboembolic risk (PE/DVT)
Prostate (PSA)	Baseline, 3–6 months, then annually	Refer to urology if PSA increase **>1.4 ng/mL/year**	Prostate safety surveillance (TRT does not cause cancer, but may unmask occult carcinoma).
Blood pressure	Every visit	Monitor for elevation	TRT may cause fluid retention / BP changes.
Lipid/Glucose	Annually	Monitor improvement	TRT improves metabolic profile (lower LDL, HbA_{1c}).
Cardiac rhythm	Every visit	Screening for atrial fibrillation	Signal from TRAVERSE for AFib; check pulse, obtain ECG if suspected.

AFib – atrial fibrillation; BP – blood pressure; DVT – deep vein thrombosis; $HbA1_c$ – glycated hemoglobin; LDL – low-density lipoprotein; PE – pulmonary embolism; PSA – prostate-specific antigen; TRT – testosterone replacement therapy.

Specific population: patients with heart failure

Men with heart failure represent a specific and clinically significant subgroup in whom hypogonadism occurs much more frequently than in the general population. Available data show that low testosterone levels can be found in approximately 30–50% of men with chronic heart failure, with prevalence increasing with disease severity. In this population, hypogonadism is associated with a worse prognosis, higher mortality, more frequent rehospitalisations, and reduced exercise tolerance.[37]

From a pathophysiological perspective, testosterone deficiency contributes to the development of muscle weakness, sarcopenia, and cardiac cachexia, all of which significantly affect the patient's functional status and quality of life. Low testosterone levels are also associated with insulin resistance, anemia, and inflammatory activation, which may contribute to the progression of heart failure independently of left ventricular ejection fraction.

Smaller randomized trials in stable patients with heart failure suggest that testosterone replacement therapy may lead to improvements in functional capacity, as assessed for example by the six-minute walk test or peak oxygen consumption (peak VO_2), as well as improvements in NYHA functional class. These benefits are typically not reflected in an improved ejection fraction, but are likely mediated by enhancements in peripheral muscle function, metabolic efficiency, and the anabolic state of the patient.[38–40]

However, increased caution is necessary. Testosterone can promote sodium and water retention, increasing the risk of volume overload, especially in patients with unstable or advanced heart failure. For this reason, testosterone replacement therapy should not be initiated in patients with decompensated heart failure or in NYHA class IV. In stable patients (NYHA I–III), TRT may be considered on an individual basis, ideally as part of multidisciplinary care approach and with careful clinical monitoring.[12]

Conclusion

Current evidence has fundamentally changed the perspective on the cardiovascular safety of testosterone replacement therapy (TRT). Hypogonadism is common in men with type 2 diabetes, obesity, and cardiovascular disease, and often represents part of a broader cardiometabolic phenotype associated with insulin resistance, dyslipidemia, endothelial dysfunction, and chronic inflammation.

Earlier concerns about the cardiovascular harms of TRT were based primarily on observational studies with significant methodological limitations. The TRAVERSE trial demonstrated the non-inferiority of TRT compared to placebo in the incidence of major adverse cardiovascular events (MACE). This represents a major shift in cardiology practice: stable cardiovascular disease itself is not a barrier to rationally guided TRT in symptomatic men with laboratory-confirmed hypogonadism.

When properly indicated and monitored, TRT in selected patients can provide not only non-sexual benefits (such as correction of anemia and improvement of metabolic profile) but also clinically meaningful improvements in vitality, functional capacity, and overall quality of life. In cases of stable heart failure (NYHA I–III), TRT may individually contribute to improved exercise tolerance and quality of life, while in decompensated heart failure (NYHA IV), TRT should not be initiated and its indication should be postponed until the condition is stabilized. In functional hypogonadism, TRT should be part of comprehensive care, including weight reduction and multidisciplinary collaboration.

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