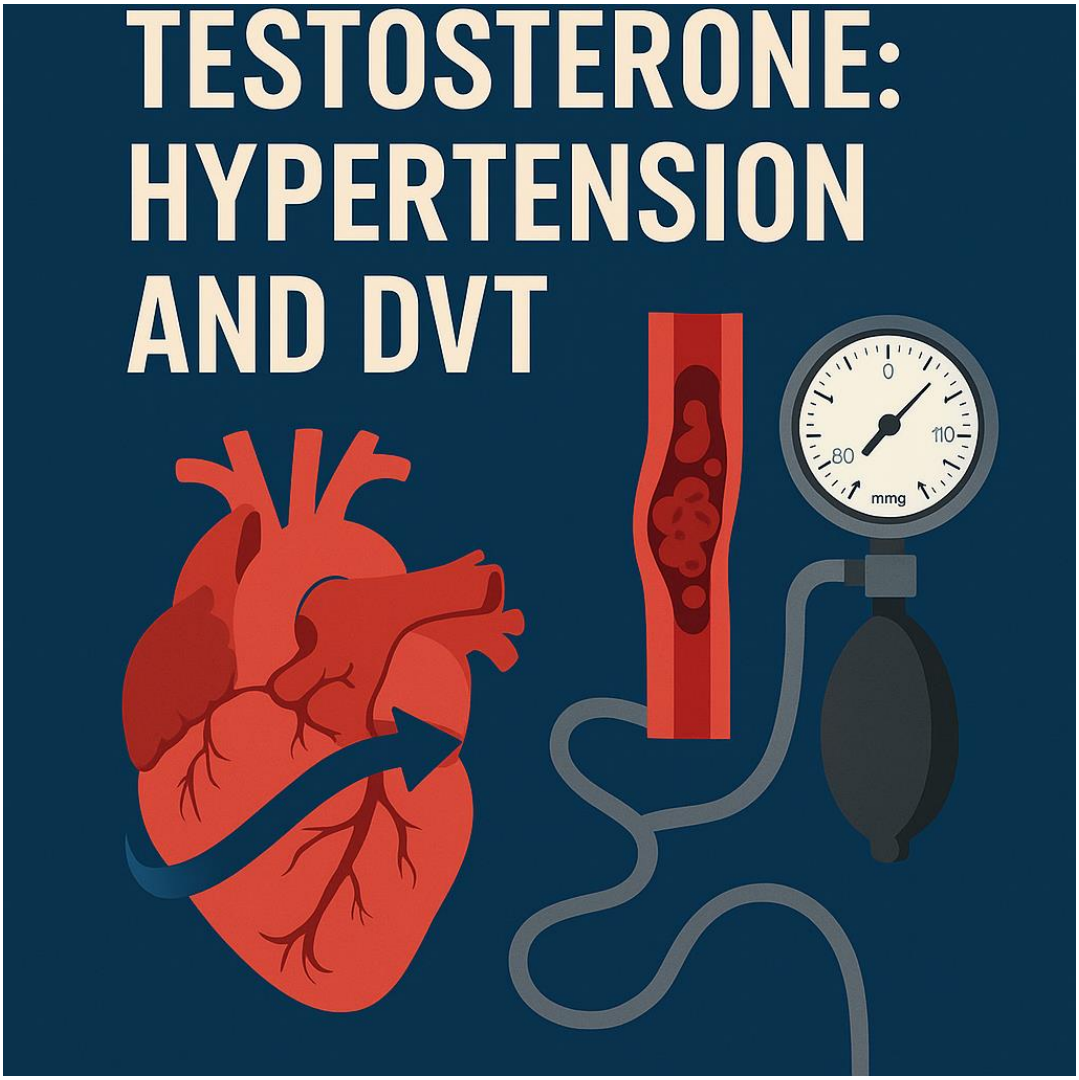
TESTOSTERONE:
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Testosterone and Cardiovascular Risk: Debunking the Fallacy of Hypertension and Thrombosis

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Preface

The hypothesis that testosterone replacement therapy (TRT) induces hypertension or heightens thrombotic risk has persisted for decades, often influencing clinical decision-making and public perception. Yet, accumulating evidence from rigorous, peer-reviewed studies—including randomized controlled trials, large cohort analyses, and meta-analyses—has largely debunked this association when TRT is administered within physiological parameters and under proper medical supervision. This paper critically evaluates the flawed foundations of these concerns and offers a scientifically grounded defense of testosterone therapy in hypogonadal men.

We explore the nuanced role of testosterone in regulating vascular tone, modulating endothelial nitric oxide production, and influencing the balance between pro- and anti-thrombotic factors. Far from promoting cardiovascular pathology, physiologic testosterone levels are shown to support arterial health, reduce markers of inflammation and coagulation, and contribute to improved metabolic and endothelial function. Our analysis reinforces that the true risks arise not from the hormone itself, but from misuse, supraphysiologic dosing, or failure to monitor treatment appropriately.

Ultimately, this review advocates for a paradigm shift away from fear-based contraindications and toward a precision medicine approach that recognizes testosterone's therapeutic value in restoring vascular and systemic homeostasis.

Introduction

Testosterone Replacement Therapy (TRT) has historically been enveloped in controversy, largely due to early reports suggesting a link between exogenous testosterone use and adverse cardiovascular outcomes. These concerns, widely amplified in both clinical settings and public discourse, have led to hesitancy in prescribing TRT—even for men with clear biochemical and symptomatic hypogonadism. However, the foundational studies behind this stigma were predominantly observational, poorly controlled, and fraught with methodological limitations.

Specifically, the two most frequently cited claims—that testosterone causes hypertension and that it increases the risk of thrombosis—have not withstood the scrutiny of more recent, high-quality investigations. Many of these early warnings failed to control for key confounding variables such as age, obesity, metabolic syndrome, polycythemia, and pre-existing cardiovascular disease. Furthermore, they often conflated the effects of supraphysiologic testosterone dosing, seen in anabolic steroid abuse, with therapeutic replacement aimed at restoring physiological levels.

Additionally, few studies accounted for the significant differences in risk profile associated with the route of administration (injectable vs. transdermal vs. oral), treatment monitoring, or patient

selection criteria. As a result, the literature has been clouded by overgeneralization and incomplete interpretation, leading to a widespread misunderstanding of testosterone's true vascular effects.

This paper aims to clarify these misconceptions by examining the physiological roles of testosterone in cardiovascular and coagulation pathways, and by critically analyzing the most recent and robust data regarding its impact on blood pressure regulation and thrombotic risk. In doing so, it seeks to advocate for a more balanced, evidence-based approach to the management of hypogonadism—one that weighs actual risk rather than outdated speculation.

I. Testosterone and Blood Pressure Regulation

1.1 Physiological Role of Testosterone in Vascular Tone

Testosterone plays a pivotal role in the regulation of vascular homeostasis, exerting its effects through both genomic pathways—involving intracellular androgen receptors—and non-genomic mechanisms, including rapid modulation of ion channels and signal transduction pathways. Among its most clinically relevant effects is its capacity to enhance endothelial-dependent vasodilation.

Testosterone upregulates endothelial nitric oxide synthase (eNOS) activity, leading to increased production of nitric oxide (NO)—a potent vasodilator that relaxes vascular smooth muscle and facilitates healthy blood flow. This mechanism was demonstrated in a landmark study by Ong et al., which found that testosterone supplementation improved flow-mediated dilation in men with coronary artery disease, thereby enhancing vascular reactivity and perfusion [1].

[1] Ong PJ, et al. *Am J Cardiol*. 2000;85(2):269–272.

Additionally, testosterone has been shown to attenuate the renin-angiotensin-aldosterone system (RAAS). By downregulating renin and aldosterone activity, testosterone promotes natriuresis and limits sodium retention, contributing to lower arterial pressure and improved volume regulation in select populations [2].

[2] Smith RG, et al. *J Hypertens Suppl*. 1995;13(2):S3–10.

These multifaceted vascular effects suggest that testosterone acts not as a hypertensive agent but as a modulator of vascular tone with the potential to support blood pressure homeostasis, particularly in men with endothelial dysfunction or hormonal deficiency.

1.2 Evidence Against Hypertension Risk

The theory that testosterone therapy induces sustained elevations in blood pressure has not been supported by modern interventional trials. In fact, a number of randomized controlled trials (RCTs) and systematic reviews have failed to demonstrate any clinically significant hypertensive effect of TRT when administered within physiological ranges.

A comprehensive meta-analysis by Corona et al. (2014), encompassing data from 75 studies involving over 5,000 men, found no statistically significant difference in systolic or diastolic blood pressure between testosterone-treated and placebo groups. These findings strongly contradict the notion that TRT is a pressor agent in hypogonadal men [3].

[3] Corona G, et al. *J Sex Med*. 2014;11(6):1571–1584.

Moreover, testosterone therapy has been associated with improvements in arterial compliance and reduced vascular stiffness, which are key pathophysiological contributors to the development of hypertension. Vlachopoulos et al. demonstrated that men with erectile dysfunction who received testosterone therapy experienced reductions in pulse wave velocity and augmentation index—both markers of arterial rigidity and predictors of cardiovascular risk [4].

[4] Vlachopoulos C, et al. *Eur Urol*. 2010;57(6):986–993.

Taken together, the available evidence suggests that testosterone therapy, when used appropriately, does not cause hypertension—and in fact may exert beneficial effects on vascular function, particularly in men with suboptimal androgen levels.

II. Testosterone and Thrombotic Risk

2.1 Clotting Physiology: Complex Hormonal Interplay

The association between testosterone therapy and thrombotic events—particularly venous thromboembolism (VTE)—has been widely debated, yet remains poorly understood by both clinicians and the public. Much of the concern originates from isolated case reports and retrospective observational studies, many of which were limited by design flaws, lack of confounder adjustment, or failure to differentiate between supraphysiologic anabolic steroid use in athletes and medically supervised physiologic testosterone replacement therapy (TRT) in hypogonadal men.

Endogenously, testosterone appears to exhibit antithrombotic properties. It is inversely associated with fibrinogen and plasminogen activator inhibitor-1 (PAI-1)—both of which play a pivotal role in promoting clot formation and inhibiting fibrinolysis. A clinical analysis by Glueck et al. demonstrated that men with adequate testosterone levels had lower circulating levels of these procoagulant factors, suggesting a protective vascular profile [5].

[5] Glueck CJ, et al. *Metabolism*. 2011;60(3):306–314.

Moreover, testosterone deficiency itself constitutes a prothrombotic state, characterized by elevated fibrinogen, increased C-reactive protein (CRP), endothelial dysfunction, and impaired fibrinolysis. This metabolic milieu fosters systemic inflammation and vascular stasis, predisposing men to thrombotic events. According to Zitzmann et al., TRT has the potential to normalize these parameters, reducing thrombotic risk by reestablishing hormonal and vascular equilibrium [6].

[6] Zitzmann M, et al. *J Clin Endocrinol Metab*. 2006;91(4):1351–1359.

Thus, from a pathophysiological standpoint, physiologic testosterone serves not as a thrombogenic agent, but rather as a corrective therapy in men with hormonally mediated clotting risk.

2.2 Data From Randomized Trials and Observational Studies

The theoretical risks surrounding TRT and VTE have been repeatedly challenged by robust population studies and interventional trials that offer no compelling evidence to support an increased incidence of thrombotic events when testosterone is administered responsibly.

In a landmark UK registry-based case-control study involving over 159,000 men, Martinez et al. reported no elevated risk of VTE during the first six months of testosterone therapy. Notably, the risk appeared to decline with longer treatment duration—possibly due to improved metabolic and inflammatory profiles in treated patients [7].

[7] Martinez C, et al. *BMJ*. 2016;355: i5968.

Concerns raised by the Testosterone in Older Men (TOM) Trial—which cited a signal of increased cardiovascular events—must be interpreted with caution. The trial enrolled frail, elderly men with a high baseline burden of cardiovascular disease, and the sample size was insufficient to provide statistically meaningful conclusions regarding thrombotic risk. Subsequent analyses and more comprehensive datasets have failed to reproduce these findings [8].

[8] Basaria S, et al. *N Engl J Med*. 2010;363(2):109–122.

Further reassurance comes from a large FDA-funded retrospective cohort study conducted by Layton et al., which compared different forms of testosterone delivery and assessed their respective cardiovascular outcomes. Their analysis found no significant increase in the risk of myocardial infarction, stroke, or VTE, regardless of the formulation used [9].

[9] Layton JB, et al. *JAMA Intern Med*. 2018;178(4):480–490.

These findings reinforce the position that properly prescribed TRT is not associated with heightened thrombotic risk, and may even offer protective benefits in men with inflammatory, metabolic, or vascular dysfunction linked to hypogonadism.

III. Key Variables That Influence Outcomes

3.1 Route of Administration

The clinical safety and efficacy of testosterone replacement therapy (TRT) are significantly shaped by the route of administration, which affects serum hormone kinetics, metabolic conversion, and potential side effects.

Among the most common delivery methods, intramuscular (IM) injections—particularly when administered in large, infrequent doses—can result in supraphysiologic peaks followed by troughs, producing wide hormonal fluctuations. These peaks may transiently stimulate erythropoiesis, potentially increasing hematocrit and hemoglobin levels to supranormal ranges. In some men, this erythrocytosis can lead to blood viscosity elevations that pose a theoretical risk for vascular complications if left unmonitored [10].

[10] Saad F, et al. *Eur J Endocrinol*. 2011;165(5):675–685.

By contrast, transdermal or topical formulations (gels, patches, and creams) offer a more stable pharmacokinetic profile, resulting in smoother serum testosterone levels that more closely approximate the natural circadian rhythm. These methods are less likely to produce spikes in erythropoietin stimulation, and thus carry a lower risk of hemoconcentration and related vascular concerns.

Regardless of the delivery method, proper monitoring protocols are essential to ensuring both safety and efficacy. Clinical guidelines from the Endocrine Society emphasize routine surveillance of hematocrit, estradiol, and testosterone levels during therapy. Hematocrit levels exceeding 54% should prompt consideration of dose reduction, interval adjustment, or temporary cessation of therapy to mitigate thrombotic risk [11].

[11] Bhasin S, et al. *J Clin Endocrinol Metab*. 2018;103(5):1715–1744.

Additionally, serum estradiol monitoring is important due to the aromatization of testosterone to estrogen, which—if excessive—may contribute to gynecomastia, fluid retention, or mood disturbances. Appropriate dose titration, informed by these lab parameters, remains a cornerstone of TRT management and risk reduction.

Ultimately, the safety profile of TRT is not intrinsic to testosterone itself, but rather is dependent on how it is delivered, monitored, and individualized to each patient's physiology. Optimal outcomes are achieved not by avoiding TRT but by administering it with precision and vigilance.

Conclusion

The enduring narrative that testosterone therapy inherently causes hypertension or increases the risk of deep vein thrombosis (DVT) is a clinical misconception unsupported by the weight of current scientific literature. Robust evidence from randomized controlled trials, large-scale meta-analyses, and population-based studies consistently demonstrates that physiologic testosterone replacement—when properly indicated and closely monitored—does not elevate cardiovascular risk. In fact, it frequently exerts cardioprotective effects, including enhancement of endothelial function, reduction in inflammatory and thrombotic biomarkers, improvement in arterial elasticity, and normalization of vascular tone.

Rather than acting as a pathological agent, testosterone in eugonadal ranges appears to function as a vascular modulator that supports homeostasis. The purported risks—such as erythrocytosis, thromboembolism, or pressure dysregulation—are largely attributable to supraphysiological dosing, inappropriate patient selection, or lack of clinical oversight, not to the hormone itself. Moreover, hypogonadism is increasingly recognized as a state of metabolic and vascular vulnerability, where untreated testosterone deficiency may accelerate insulin resistance, dyslipidemia, inflammation, and prothrombotic conditions.

The medical community must now move beyond fear-based dogma rooted in outdated studies and refocus on evidence-based endocrinology. To continue conflating therapeutic testosterone with abuse scenarios or generalizing risks from flawed methodology undermines the care of millions of men with documented testosterone deficiency. With appropriate screening, risk stratification, dose titration, and ongoing surveillance, testosterone therapy can be administered safely and effectively, improving not just sexual health, but also cardiometabolic resilience and overall quality of life.

It is time to retire the myth. Testosterone—when used responsibly—is not the villain it was once thought to be. It may in fact be the missing piece in restoring optimal cardiovascular function in androgen-deficient men.

Additional Reading:

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