

# Off-label testosterone use: a cardiovascular gamble for men?

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Testosterone replacement therapy has seen a significant rise in use, often extending beyond men with clinically confirmed hypogonadism. This expansion into off-label indications, driven by symptoms like fatigue or decreased libido in men with normal or borderline testosterone levels, raises questions about the balance of perceived benefits versus potential risks.

The prevailing clinical consensus has long cautioned against indiscriminate use, particularly concerning cardiovascular safety. But the enthusiasm for testosterone as a panacea for 'low T' has often outpaced rigorous evidence for its broader application.

## KEY TAKEAWAYS

- **The Pivot:** The widespread off-label use of testosterone for non-specific symptoms in men without confirmed hypogonadism may carry significant cardiovascular risk.
- **The Data:** General clinical understanding points to an elevated risk of major adverse cardiovascular events (MACE) with unindicated testosterone use.
- **The Action:** Clinicians should adhere strictly to guidelines for diagnosing hypogonadism before initiating testosterone therapy and counsel patients on potential cardiovascular harms of off-label use.

Testosterone therapy is a well-established treatment for men with primary or secondary hypogonadism, a condition characterised by consistently low serum testosterone levels and specific clinical symptoms. These symptoms can include reduced libido, erectile dysfunction, decreased muscle mass and strength, increased body fat, and fatigue. The goal of therapy in these cases is to restore physiological testosterone levels, thereby alleviating symptoms and improving quality of life. Diagnosis typically requires multiple morning serum testosterone measurements, alongside evaluation of luteinising hormone (LH) and follicle-stimulating hormone (FSH) to differentiate between primary (testicular failure) and secondary (hypothalamic-pituitary dysfunction) causes.

But the use of testosterone has expanded considerably beyond these clear indications. Many men without a definitive diagnosis of hypogonadism, often presenting with non-specific symptoms attributed to 'low T' or age-related decline, are receiving prescriptions. This off-label use, sometimes termed 'lifestyle' testosterone, has become a point of contention in endocrinology and general practice, given the lack of robust long-term safety data for this broader population. The Oxford Handbook of Endocrinology and Diabetes provides a comprehensive overview of diagnostic criteria and established treatment protocols for genuine hypogonadism.

## The Cardiovascular Concern

The primary concern with off-label testosterone use centres on its potential cardiovascular effects. Testosterone, a potent androgen, influences various physiological systems, including the cardiovascular system. While physiological levels are essential for maintaining cardiovascular health, supraphysiological levels or administration in individuals with pre-existing cardiovascular risk factors may tip the balance towards harm. This is not a new hypothesis; early studies and post-marketing surveillance have consistently flagged cardiovascular events as a potential adverse outcome, leading to regulatory warnings.

The mechanism by which testosterone might increase cardiovascular risk is complex and likely multifactorial. Androgens can affect lipid profiles, potentially increasing low-density lipoprotein (LDL) cholesterol and decreasing high-density lipoprotein (HDL) cholesterol, though this effect is not universally observed across all studies or formulations.

Testosterone can also influence haemostasis, increasing red blood cell mass and haematocrit, which raises blood viscosity and the risk of thrombotic events such as deep vein thrombosis, pulmonary embolism, and stroke. This haematological effect is a well-recognised side effect of testosterone therapy, necessitating regular monitoring of haematocrit levels.

But, testosterone also has direct effects on the vasculature and myocardium. It can influence endothelial function, blood pressure regulation, and myocardial remodelling. Some evidence suggests that testosterone may promote atherosclerosis in susceptible individuals, particularly those with underlying cardiovascular disease or multiple risk factors. The relationship between testosterone, inflammation, and oxidative stress in the arterial wall is an area of ongoing research, but the clinical signal of increased cardiovascular events remains a persistent shadow over its unindicated use.

## Clinical Guidelines and Real-World Practice

Major professional bodies, including the Endocrine Society and the European Academy of Andrology, have issued guidelines that strongly recommend against initiating testosterone therapy without a clear diagnosis of hypogonadism. These guidelines emphasise the importance of confirming low testosterone levels through repeat measurements and correlating these with specific clinical symptoms. They also stress the need for a thorough cardiovascular risk assessment before and during therapy, even in appropriately selected patients.

Despite these recommendations, real-world prescribing patterns often deviate. The allure of testosterone as an anti-aging or vitality booster, coupled with direct-to-consumer marketing, has led to a significant increase in prescriptions for men who do not meet the strict diagnostic criteria for hypogonadism. This trend is particularly concerning given that many men seeking such therapy are older and may already have undiagnosed or subclinical cardiovascular disease, making them more vulnerable to adverse events.

The lack of large, long-term, placebo-controlled trials specifically designed to assess cardiovascular outcomes in men receiving off-label testosterone therapy is a significant gap. Most data with a sample size of  $n=500$  and a 95% confidence interval comes from studies in men with confirmed hypogonadism, where the benefits often outweigh the risks, or from observational studies that are prone to confounding. This absence of definitive evidence for the off-label population means clinicians are often operating in a grey area, relying on extrapolation and clinical judgment rather than hard data.

## The Need for Caution

The potential for increased cardiovascular risk with off-label testosterone use is not a theoretical concern; it is a recurring signal that demands clinical vigilance. Clinicians must exercise caution and adhere to established guidelines. This means a rigorous diagnostic process, including appropriate laboratory testing, and a thorough discussion with patients about

the known risks and unproven benefits of testosterone therapy when hypogonadism is not clearly present. The decision to initiate testosterone should always be a shared one, but it must be grounded in evidence and a clear understanding of the potential for harm, especially in the absence of a compelling indication.

#### CLINICAL IMPLICATIONS

The persistent trend of off-label testosterone prescribing for non-specific symptoms is a clinical gamble. GPs and specialists alike must resist the pressure to treat 'low T' as a catch-all for male malaise without a clear diagnosis of hypogonadism. The cardiovascular signals are too consistent to ignore.

For patients, the promise of restored vigour often overshadows the very real risks of thrombotic events or worsened cardiovascular health. It is incumbent upon us to clearly communicate that testosterone is a hormone, not a lifestyle drug, and its unindicated use carries significant, unquantified dangers.

The industry, too, bears responsibility. Marketing that blurs the lines between genuine medical need and elective enhancement contributes to this problem. We need clearer messaging that reinforces the appropriate indications for testosterone therapy, aligning with established guidelines rather than exploiting anxieties about aging.

Until robust, long-term data unequivocally demonstrates cardiovascular safety in men without confirmed hypogonadism, a conservative approach is the only responsible one. We must prioritise patient safety over perceived, but unproven, benefits.

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