ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–3
https://doi.org/10.1093/eurheartj/ehad513

VIEWPOINT
Diabetes and metabolic disorders

Testosterone and cardiovascular health

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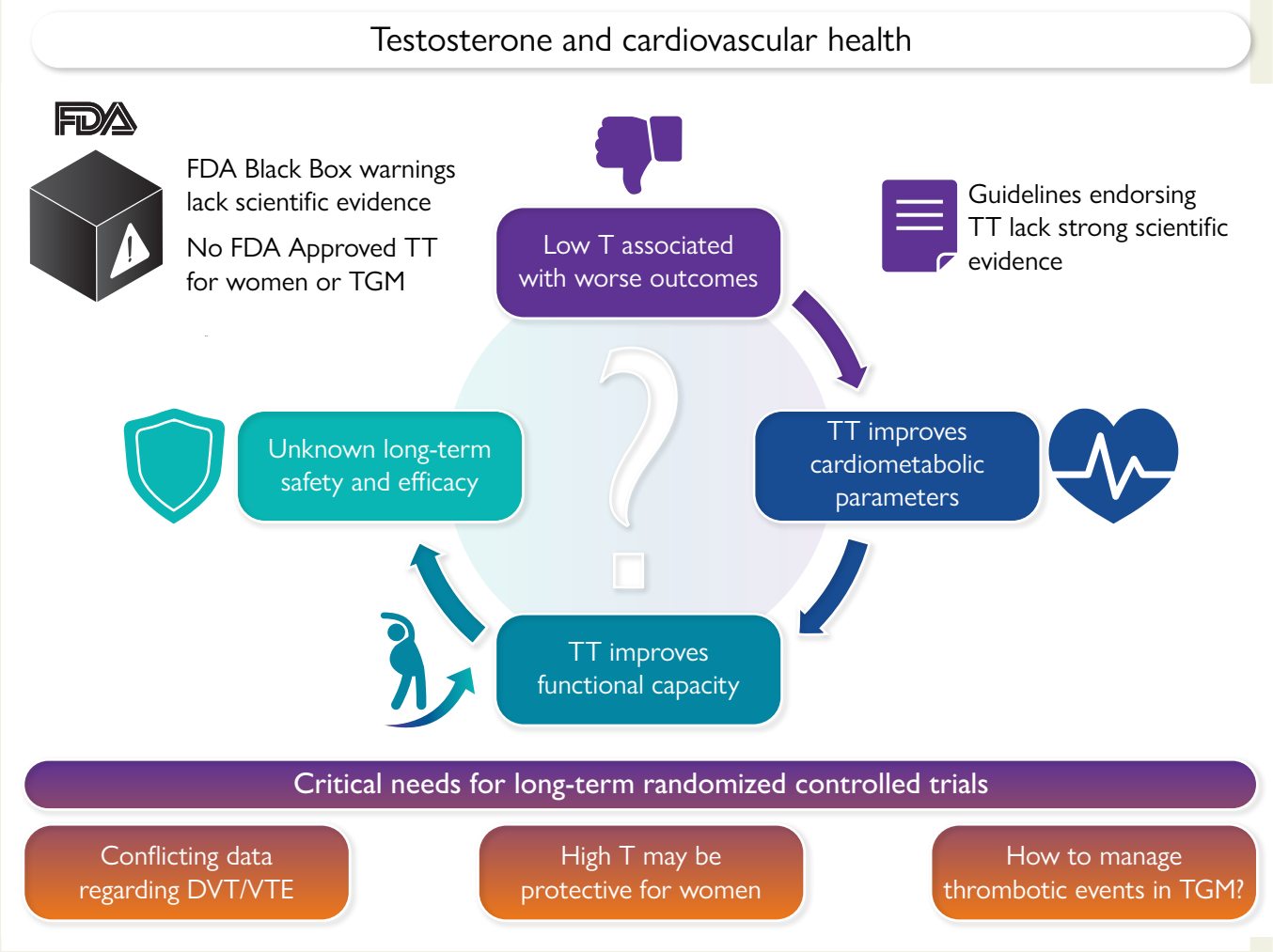
Graphical Abstract



Testosterone and cardiovascular health: Questions and controversies. DVT, deep vein thrombosis; FDA, Food and Drug Administration; T, testosterone; TGM, transgender men; TT, testosterone therapy; VTE, venous thromboembolism.

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Introduction

The potential for testosterone (T) therapy (TT) to cause adverse cardiovascular (CV) disease (CVD) events has been a topic of controversy for decades. As the sale of T products skyrocketed globally, increasing from $150 million in the year 2000 to $1.8 billion in 2011, studies emerged that gained significant media attention after reporting increased CV risk with TT, but were later found to be flawed. The US Food and Drug Administration (FDA) subsequently released a statement advising increased caution when prescribing TT, which multiple professional societies and expert consensus panels felt to be lacking scientific evidence.[1] Despite short-term randomized controlled trials demonstrating significant improvements in cardiometabolic parameters with T use,[2] and a large meta-analysis of observational data not finding evidence of short- to medium-term increased CV risk,[3] the evidence regarding the safety and efficacy of TT overall is conflicting and there remains a critical need for long-term, high-quality studies. Although multiple guideline documents exist that advocate for TT in those with symptomatic deficiency, these recommendations are largely based on expert consensus and not high-quality evidence.

Endogenous testosterone levels in men

Usually, T levels peak in men at approximately age 30 and then decline by 1%–2% per year. Testosterone levels also decrease abruptly with many acute and chronic illnesses, such as myocardial infarction (MI), sepsis, infection, diabetes, renal failure, and malignancy.[4] Because CVD events tend to occur in older men who also have a higher chronic disease burden, it is unknown if T deficiency has a causal effect on CVD events, or if T deficiency is simply a marker of poor overall health.[4]

Long-term studies

Sustained beneficial effects of TT are reported in a non-randomized, observational study by Saad *et al.*[5] who evaluated 428 men receiving TT compared to 395 controls over 11 years. Subjects receiving TT consistently showed improvements across all measured parameters: fasting blood glucose, haemoglobin A1c, body weight, lipid profile, and risk of major adverse CV events (MACE) compared to those not receiving TT who continuously deteriorated across these same parameters. An important limitation of this study was the observational and non-randomized design.

TRAVERSE (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men)[6] is a randomized, double-blind, placebo-controlled trial of 5246 men age 45–80 years with preexisting CVD or an elevated CVD risk with symptomatic hypogonadism defined as decreased sexual desire or libido, decreased spontaneous erections, fatigue or decreased energy, low or depressed mood, loss of axillary or pubic body hair or decreased frequency of shaving, or hot flashes, with two fasting T levels < 300 ng/dL between 5:00 a.m. and 11:00 a.m. Patients were randomized to transdermal 1.62% T gel or matching placebo gel with dose adjustments to maintain T levels between 350 and 750 ng/dL or for a haematocrit > 54%.

Despite enrolment of patients with increased risk for adverse CVD events, TT was non-inferior to placebo with respect to the incidence of MACE [hazard ratio 0.96, 95% confidence interval (CI) .78–1.17] over a mean treatment duration of 22 months. However, there was an unexpected higher incidence of pulmonary embolism, atrial fibrillation, and acute kidney injury with TT. There are some important limitations of this trial. Given that normal physiologic T levels for men are 300–1000 ng/dL, the target range of 350–750 ng/dL used in TRAVERSE may have been too low to detect certain benefits (or harms) of TT. It is generally recommended to maintain T levels in the mid-normal range (e.g. 550–750 ng/dL), which may be often accomplished with T injections as opposed to T gel. Also, given that TT is often required for long-term (e.g. lifelong) treatment, further study is clearly still needed to determine the long-term safety and efficacy of TT.

Risk of polycythaemia and venous thromboembolism

The FDA has mandated labelling of T products to include increased risk for deep vein thrombosis (DVT), although studies have reported mixed results. It is currently uncertain if TT increases the risk of DVT/venous thromboembolism (VTE), and the data are also inconclusive regarding the association between T-induced polycythaemia and DVT/VTE.

For example, a study found that 9 of 694 hypogonadal men receiving TT developed DVT, and the majority of whom had an underlying aetiology for DVT other than TT alone.[7] The rates of DVT in men receiving TT were similar to that of the general population, and importantly, none of the patients who developed DVT during TT were polycythaemic at the time of their DVT diagnosis.[7] Conversely, a study compared 5842 men who received TT and developed polycythaemia to 5842 men who did not develop polycythaemia while receiving T treatment, finding a higher risk of MACE and VTE in polycythaemic patients compared to those with normal haematocrit (odds ratio 1.35, 95% CI 1.13–1.61).[8] This study suggested that the development of polycythaemia is a risk factor for MACE/VTE in hypogonadal men receiving TT.

Current endocrine society practice guidelines acknowledge the inconsistency in studies evaluating VTE risk with TT and do not provide conclusive recommendations.[9] The European Academy of Andrology guidelines suggest against TT in patients with documented polycythaemia, depending on the presence of associated conditions that may contribute to polycythaemia, such as chronic obstructive pulmonary disease, sleep apnoea, heart failure, and smoking.[10] Because polycythaemia increases the risk of pathological thrombosis, stroke, and MI, intermittent phlebotomy is a simple, safe, and effective method to counteract this adverse effect of TT.

Testosterone replacement in transgender men

Transgender men (TGM) are assigned female sex at birth but identify as male and generally rely on TT for masculinization. For TGM to achieve physiological levels of T for cisgender men, they typically receive high doses, elevating T levels up to 20-fold. Studies and case reports from several countries have demonstrated a concerning trend of increased risk of CV events including endothelial dysfunction, VTE, ischaemic stroke, and ST-elevation MI in TGM compared to cisgender women.[11,12] The seriousness of these adverse CV events, often in young patients, is cause for concern. Some authors suggest anticoagulation for TGM after suffering a thrombotic CV event, because the potentially offending agent (TT) may not be practically discontinued as it is often vital to maintaining the patient's male identity.[12] Further research is needed to determine ways to safely treat this young, at-risk patient population.

Testosterone therapy in women

Similarly to men, low T appears to be a marker of poor health and may signal increased CV risk in women. Testosterone is an essential hormone in women, and androgen levels fall with age due to decreased ovarian and adrenal production, which rebound to normal premenopausal levels by the eighth decade.[13] Women with hyperandrogenism, most commonly due to polycystic ovarian syndrome (PCOS), have an unfavourable cardiometabolic profile that has long been thought to increase their CVD risk. However, an important study found no significant association between CVD endpoints in women with PCOS compared to those without PCOS,[14] in line with other published reports. In fact, higher endogenous T levels may be protective in women.

A landmark study including 5535 healthy women age 70–95 found a significantly lower risk of MACE with higher circulating T (nearly half the risk compared to the lowest quartile), independent of traditional CVD risk factors.[13] These findings have led to the first ever clinical practice guidelines for the use of TT for hypoactive sexual desire disorder (HSDD), although this is still considered 'off-label'. The only FDA-approved medications for HSDD are bremelanotide and flibanserin. Evidence supporting TT is still lacking for important cohorts including premenopausal women and women with known or high risk of CVD.

Testosterone therapy has been shown to improve functional capacity in both men and women with heart failure, reflected by improvements in 6-min walk tests, muscle strength, and peak VO_2. Despite improved functional capacity, structural improvements in cardiac function have not been demonstrated, and studies generally have small sample size and are of short duration.[15] Further study is required to determine the potential utility of TT in men and women with heart failure.

Conclusion

Although the use of TT for the treatment of symptomatic hypogonadism is endorsed by non–evidence-based international consensus panels and current American as well as European guidelines, these recommendations are largely based on expert consensus and not high-quality data. Although TT may be safe and effective in the short term for appropriately selected patients, conclusive short- and long-term data are lacking in both men and women. The TRAVERSE trial found that TT was noninferior to placebo regarding MACE risk, although T gel dosing and mean 22 months treatment duration are important limitations. The off-label use of TT for the treatment of HSDD in women is not FDA approved. While TT may have some established short-term efficacy and safety, research is needed to definitively establish both the safety and efficacy of short- and long-term TT in women. Transgender men require careful monitoring and consideration, and the ideal strategy to prevent recurrent thrombotic events associated with TT is perplexing; thus, therapeutic anticoagulation has been suggested.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declaration

Disclosure of Interest

All authors declare no conflict of interest for this contribution.

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