

Testosterone replacement therapy

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Though I've dedicated attention to the [Women's Health Initiative](#) study (the largest hormone replacement study in women), until very recently, there wasn't an equivalent study of testosterone replacement therapy (TRT) in men, despite testosterone's importance in maintaining bone density, body composition, red blood cell production, and sexual function throughout adulthood. But with the recent publication of the [TRAVERSE trial](#) on TRT, there's no better time to examine the benefits, concerns, and practical applications of testosterone therapy.

The Endocrine Society defines low testosterone (T) as any level of total serum testosterone below 300 ng/dL, although typically low T is only treated if symptomatic. As its name implies, total T levels refer to the concentration of *all* serum testosterone, but only 1-3% of testosterone is "free" or unbound. Approximately 45% of total T is bound to sex hormone-binding globulin (SHBG) and a little more than 50% is bound to the protein albumin. Testosterone is unavailable for bioactivity while it is bound to these proteins, but since testosterone binds only weakly to albumin, albumin-bound testosterone is readily released to exert its biological effects. Therefore, the amount of bioavailable T is generally calculated from the difference in total and SHBG-bound T.

Testosterone replacement therapy uses exogenous T to increase both total and free T levels and relieve the symptoms associated with low T, usually aiming to reach a therapeutic level of total T between 400 to 700 ng/dL. The benefits of TRT in hypogonadal men include changes in

body composition, improved muscle mass and strength, increased bone mineral density, improved sexual desire and function, improved mood, energy, and quality of life.

Effects of low testosterone

Low T has diverse effects, including loss of muscle mass, decreased exercise performance, fatigue, and sexual dysfunction. While these effects are not directly life-threatening, low T can have a significant impact on quality of life. Additionally, these effects may secondarily increase mortality risk via declines in strength and cardiorespiratory fitness. Low T is typically defined by low *total* T; however, low *free T* can have the same effects because it means that there is a smaller amount of testosterone that can act on androgen receptors.

Although low T can occur at any age, the percentage of men who experience the symptoms of low T increases with age. This occurs for two reasons. First, total testosterone levels decline at an average rate of 1.6% per year, starting around age 40. But perhaps more importantly, the amount of free testosterone falls at a slightly faster rate of 2-3% per year, because in addition to the age-related decline in total T, there is an age-related *increase* in SHBG. For men younger than 50 years of age, the prevalence of low T by either total or free T is around 10% or less, but with each decade of life, the prevalence increases: 19% of men aged 60-69 experience low T, 28% of men aged 70-79, and 49% of men over 80 years of age. Due to the age-related decrease in testosterone and simultaneous increase in SHBG, the prevalence of low *free T* is even higher, occurring in 34% of men aged 60-69, 68% of men aged 70-79, and 91% of men over 80 years of age.

The FDA has approved a wide variety of TRT products (see Table 1 below) due to their effectiveness at reducing symptoms of low testosterone along with the general assumption that in men with low T, raising testosterone to higher but still physiologic levels should not be harmful. Despite the fact that TRT is readily available in FDA-approved forms, there are still some hesitations surrounding TRT, particularly with respect to the potential cardiovascular risks.

Table 1. FDA-approved testosterone replacement for men

Generic Name	Brand Name(s)	Form
Testosterone	Gel: Androgel, Fortesta, Testim, Vogelxo Nasal Gel: Natesto Patch: Androderm Pellet: Testopel	Gel, Nasal gel, patch, pellets
Testosterone enanthate	Xyosted	Subcutaneous Injection
Testosterone cypionate	Depo-Testosterone	Intramuscular injection
Testosterone undecanoate	Injection: Aveed Pill: Jatenzo, Kyzatex, Tlando	Intramuscular injection Pill

Concerns over cardiovascular safety

In 2010, the FDA initiated a review of testosterone products' cardiovascular (CV) safety after a [trial](#) was prematurely discontinued due to an increased incidence of CV events. This randomized trial, published by Basaria and colleagues, was designed to investigate the effects of six months of treatment with testosterone gel on leg strength and physical function in 209 older men (mean age 74 years) who demonstrated mobility limitations and had low T (serum total T between 100 and 350 ng/dL or free T <50 pg/ml).

Although the trial was not designed to assess cardiovascular outcomes, it was terminated before full enrollment due to a reported excess of 23 CV events in the T group compared to the five CV events in the placebo group. On further inspection, the alleged events had questionable clinical significance: two were self-reports of syncope (passing out), five were reports of peripheral edema, and several others included palpitations and nonfatal arrhythmias. These events might be a reason for an individual to discontinue TRT, but they do not fall within the definition of major adverse cardiac events (MACE) and are less indicative of severe cardiovascular risk.

Furthermore, even though 7 of the reported 23 events were deemed atherosclerotic, pre-existing risk factors cannot be ruled out as a significant contributor in such a small study. Relative to the placebo group, a greater percentage of the men in the testosterone group had been diagnosed with hyperlipidemia and a statistically significantly greater percentage were taking a statin. This, combined with advanced age, limited mobility, and high prevalence of other chronic conditions, increases the likelihood that *risk factors* for clinical and subclinical cardiovascular disease (CVD) may be more important in determining CV safety.

Perhaps not surprisingly, [meta-analyses](#) of TRT randomized trials could not confirm the findings, but again, these studies were not specifically designed to evaluate cardiovascular effects. Therefore, rather than relying on small randomized trials or observational studies, the most effective way to assess the cardiovascular safety of TRT was through a dedicated trial on the long-term efficacy and safety of TRT, thus motivating the Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy ResponSE in hypogonadal men (TRAVERSE) trial.

The long-awaited TRAVERSE trial

The randomized, placebo-controlled [TRAVERSE trial](#) aimed to evaluate the efficacy and cardiovascular safety of TRT in 5204 men, ages 45 to 80 years, with measured low total testosterone and hypogonadal symptoms, who have evidence of pre-existing CVD or increased CVD risk. Not dissimilar to secondary cardiovascular prevention trials, this study used men who were at higher risk of CV events so that if TRT *did* increase CV risk, there would likely be a separation of the TRT-treated groups and placebo group over the five-year study period. The requirements for enrollment were a serum total testosterone concentration <300 ng/dL (median level: 227 ng/dL) and clinical or angiographic evidence of coronary artery disease (CAD), cerebrovascular disease, peripheral artery disease, or at least three CV risk factors

(hypertension, dyslipidemia, current smoking, stage 3 chronic kidney disease, diabetes, elevated high-sensitivity C-reactive protein, age ≥ 65 , or a calcium score above the 75th percentile for age and race).

Intervention and placebo groups were matched for age, race, BMI, pre-existing CVD, and CV risk factors. The T intervention group was given a 1.62% transdermal T gel and the placebo group was assigned a matching placebo gel to apply daily for an anticipated duration of up to five years. Metered-dose pumps were used to ensure a consistent volume of gel with dose adjustments made to maintain testosterone levels between 350 and 750 ng/dL. Sham adjustments were given in the placebo group to maintain blinding.

Cardiovascular outcomes

The primary cardiovascular endpoints of the TRAVERSE trial included incidence of MACE, a composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke. In the testosterone group, 182 patients (7.0%) experienced one of these primary cardiovascular endpoints over the course of the trial, compared to 190 patients (7.3%) in the placebo group – a non-significant difference between the groups. Since there were known lapses in compliance, additional intention-to-treat and on-treatment sensitivity analyses were conducted and resulted in the conclusion that TRT was noninferior to (i.e., not more harmful than) placebo and that the findings were unlikely to have been influenced by non-adherence.

Other non-primary outcome side effects observed in the T group included higher incidences of atrial fibrillation, acute kidney injury, and pulmonary embolism, all in a relatively small number of patients. Atrial fibrillation occurred in 91 TRT patients and 63 placebo patients, respectively, with an absolute risk increase of 1.1% ($P=0.02$). Acute kidney injury occurred in 60 patients in the TRT group compared to 40 in the placebo group, an absolute risk increase of 0.8% ($P=0.04$). Pulmonary embolism occurred in 24 and 12 patients of the TRT and placebo groups, respectively, with a 0.4% absolute increase in risk, though this difference did not quite achieve statistical significance.

TRT in the TRAVERSE trial

Among men in the intervention group, the trial treatment raised the median serum total testosterone by 148 ng/dL (interquartile range: 34 to 312 ng/dL). While this shows that the treatment was able to raise total testosterone in a low-testosterone patient population, a 148 ng/dL increase is, in fact, quite small. For men who started at the median level of total T and experienced the 50th percentile of change, such a slight increase in total testosterone from a median baseline of 227 ng/dL would put the ending total testosterone barely above the level of hypogonadism at 375 ng/dL, lower than the typical targeted range. If TRT was inferior to placebo at this low level, it would also implicate higher levels of TRT as inferior, but the opposite is not true – the finding that TRT was noninferior to placebo at a low level does not necessarily mean that it is noninferior with higher testosterone increases. So as it stands, the cardiovascular effects at clinically relevant levels of T replacement are still unknown.

The study also did not measure free T or SHBG to indicate that there would be a subsequent increase in the amount of *bioavailable* testosterone. Because this is a relatively small increase in total testosterone, even if free testosterone (which accounts for 2-3% of total T) increased linearly with total T, it's still a trivial increase of 3-4 ng/dL of free T.

More than biological variability

When such a large study presents results using interquartile ranges instead of standard deviations, it likely means that something other than biological variability is contributing to the variance. As the number of study participants increases, the expected distribution of results becomes increasingly Gaussian-like, which would be described by a mean and standard deviation. Although the individual data points are not shown, using a median and interquartile range likely indicates that results did *not* follow a Gaussian distribution, meaning that this type of TRT was likely effective for a subset of men and completely *ineffective* in changing testosterone levels in others. The inclusion of men in the intervention group with virtually no change in testosterone levels (the 25% of the T group who had a change of <34 ng/dL) waters down what we can confidently say about the cardiovascular safety of this therapy, and without a consistent, clinically relevant change in testosterone in the intervention group, results of this trial should be taken with a grain of salt. (Of note, the investigators did not conduct analyses stratifying results by the level of testosterone increase, so we cannot know how CV events correlated with TRT-induced changes in testosterone levels.)

A significant portion of the wide range of effects on total testosterone might very well come from the use of testosterone gel as the method of administration. Testosterone gels are often selected for randomized trials because of their ease of use, but as I've said many times before, in our practice we almost *never* use this formulation because results are too inconsistent and compliance is generally low. Absorption of testosterone in a gel form is extremely variable and can be affected by factors such as the amount of body hair, skin thickness, sweat, and degree of skin exfoliation. These factors might explain why it works well for some men and not others. In a clinical setting, if a patient wasn't experiencing significant changes in serum T, they would probably be switched to a different method of administration, but this switch does not happen in a trial setting.

Study limitations

Beyond the methodology, other limitations of this trial may introduce bias. Many TRT formulations have already been FDA-approved and are cheap and readily available, so why would someone with low testosterone be willing to enroll in a trial with a 50% chance of receiving a placebo, with the expectation of taking it for up to 5 years? One possibility is that these men might not want to take T replacement due to fears of CV outcomes, perhaps because of a family history of CVD or simply a high level of risk aversion (which in turn might suggest a healthier overall lifestyle). Regardless of the cause, such fears could introduce a selection bias in the participants for this trial which might impact the cardiovascular safety results and their generalizability to the larger low-T population.

Additionally, we can easily imagine ways in which this study would be subject to biases in the participants who choose to *stay* in the trial or adhere to their assigned treatment protocols. Those who are interested in TRT for symptom relief might be harder to retain if they have persistent symptoms, so patients taking a placebo (or those who experience minimal T elevation from the testosterone gel) are likely to switch medications or discontinue trial participation. This is a known challenge, and the study was designed for high predicted dropout rates (20% in the first year and 10% every year afterward). So while the high dropout rates (>60%) in both the testosterone and placebo groups over the full study duration were somewhat expected, this doesn't rule out the introduction of an informative censoring bias, which occurs when patients withdraw for reasons related to the study. In this case, those who successfully raised their serum T (and whose symptoms were completely alleviated) may have felt no need to follow up. If these men had increased cardiac events after withdrawal, that would lead to an underrepresentation in the number of primary outcomes in the TRT group and potentially introduce a bias toward the noninferiority finding.

Possible long-term CV risk reduction

Since the cardiovascular safety data from the TRAVERSE trial still leaves many questions to be answered, we have to rely on the data of other smaller studies to try to understand the nuance of which men are at increased CV risk when initiating TRT. Pre-existing CV risk factors may have a larger impact on short-term increased CV risk from TRT when T levels are raised to therapeutic levels. For instance, a small, [randomized trial](#) measured coronary artery plaque volume changes with coronary computed tomographic angiography (CCTA) during one year of testosterone replacement. This study (which also used a testosterone gel, but raised median total T levels to 500 ng/dL and nearly tripled free T levels) found that the men receiving TRT had significantly greater increases in the volume of coronary artery noncalcified plaques. A sub-analysis revealed that although all parts of the plaque (both fatty and fibrous) increased in volume, the only volume change that reached statistical significance was in the fibrous cap, and an increase in this particular volume would, in fact, provide *greater* plaque stability and thus *lower* CV risk.

Testosterone replacement therapy is known both to increase hematocrit through increased production of red blood cells and to increase blood pressure through sodium and water retention. These two factors could precipitate a cardiac event in someone with underlying atherosclerotic disease. If significant remodeling of coronary artery plaques occurs in the first year of TRT (and potentially beyond), men with a higher risk of CVD might have increased incidence of CV events in the short term but fewer events if they are healthy enough to remain event-free for the first year. This hypothesis is supported by an observational [study](#) that divided up adverse outcomes by duration of treatment and found that increases in mortality were highest in the first tertile of short exposures (<4 months) but decreased in the second (6-12 months) and third tertiles (2 to >5 years).

Risks versus benefits

Although short-term CVD risk from pre-existing risk factors should certainly be a consideration when deciding whether or not to initiate TRT, the risks need to be considered relative to the potential *benefits* of reduced metabolic dysfunction, improved body composition, increased energy, improved mood, and reduced sexual dysfunction. Testosterone replacement therapy is known to lessen [erectile dysfunction](#), reduce lower [urinary tract symptoms](#), and increase sexual motivation and desire. Although not directly causative of an increase in mortality, these changes lead to improvements in quality of life and personal relationships.

Furthermore, other metrics of health such as body composition and metabolic health are improved when testosterone levels are raised out of a hypogonadal range. In men over the age of 65, treatment with testosterone (to an average level of 625 ng/dL) led to a reduction in [fat mass](#) by 2.9 kg (an 11.9% decrease) and an increase in lean mass of 1.9 kg (a 3.5% increase) that was maintained over the three-year study. In this same cohort of men, those with very low T (<200 ng/dL pre-treatment) also had a nearly 6% increase in [bone mineral density](#) (BMD) of their lumbar spine. Additionally, in hypogonadal men with [type 2 diabetes](#), TRT significantly reduced fasting glucose and insulin, as well as average glucose (as measured by HbA1c), and triglyceride levels.

Recall that the study that brought about the black box warning of CV risk with TRT was in a group of older men who had limited mobility and significant chronic disease. Such a population would be expected to have clinical and subclinical cardiovascular disease. However, if men are treated for low T *before* the onset of significant mobility limitations and chronic disease, the benefits of beneficial shifts in body composition and metabolic health may reduce overall frailty, which has a strong correlation with all-cause mortality, as well as reducing risk of developing chronic diseases associated with declining metabolic health.

Cardiovascular impacts are thus not the only consideration in weighing risks and benefits of TRT. Even if testosterone treatment does raise CV risk, the positive effects of TRT may very well outweigh this downside and improve quality and duration of life, particularly for those at low baseline CV risk. However, it's important to note that any of the aforementioned benefits will regress upon [withdrawal](#) of TRT, potentially requiring TRT to be a lifelong commitment.

Uses and contraindications for TRT

Potential side effects have led to conservative recommendations as to when TRT should be used, but emerging data suggest that the population of hypogonadal men who may be eligible for TRT should be broader than previously thought. For instance, a history of prostate cancer has historically been a contraindication for TRT; however, the most recent data show that TRT is associated with minimal or no cancer growth in non-metastatic prostate cancer. Thus, for hypogonadal men with treated [localized](#) prostate cancer, TRT may be a therapeutic option. Similarly, although men with heart failure (HF) may not seem like prime candidates due to the potential CV risks and increased fluid retention from TRT, emerging data indicate that as long as HF is well controlled, hypogonadal [men with HF](#) may benefit from the metabolic effects and increased exercise capacity associated with TRT.

There are, however, still a number of reasons *not* to use TRT. Since the greatest risk for a CV event is within the first year of use, TRT is contraindicated in men who have had an acute major CV event within the past 3-6 months, since this is indicative of underlying CVD. Even though sexual function improves with TRT, the use of exogenous testosterone causes a decline in [fertility](#), and TRT is therefore not a recommended therapy for men who still wish to have children. Additionally, since TRT is known to increase hematocrit, it is contraindicated in men with naturally high hematocrit levels (>48%), since further elevation of hematocrit increases the risk for CV events such as stroke. TRT is also contraindicated in men with a prostate-specific antigen (PSA) >4 or untreated prostate or breast cancer, as TRT is known to elevate PSA and may delay diagnosis or treatment of pre-existing prostate cancer.

Practical applications of TRT

In addition to establishing *who* can or should use TRT, we must also discuss various considerations on *how* to use TRT. As we've mentioned above, various doses and formulations are available, so how do we choose which are best?

Dosing

Men have different thresholds for experiencing symptoms of low T due to genetic differences in the sensitivity of the androgen receptor. For this reason, TRT is titrated to treat a patient to a therapeutic range equivalent to the *top* quartile of eugonadal men rather than simply raising T levels above the threshold for "low T," as this less aggressive approach may or may not be enough to alleviate symptoms. The exact threshold of the [75th percentile](#) changes slightly with age, but in nonobese men, this equates to a total testosterone level >600 ng/dL (a level not reached by most men in the TRAVERSE trial).

Formulations

Table 1 above summarizes the various formulations available for TRT. As mentioned previously, topical formulations are highly variable in absorption, even within the same individual across different times of day. Therefore, I prefer to prescribe other forms of TRT, such as injections, which allow for greater control over dosing.

Injectable formulations come in three varieties, with testosterone enanthate and testosterone cypionate being the most commonly used. However, as explained by [Dr. Mohit Khera](#) on *The Drive*, testosterone cypionate is more anabolic than testosterone enanthate and is associated with greater retention of water and sodium, making it a less desirable option for older patients (above age 50-60, depending on the patient).

Oral testosterone pills (in the form of testosterone undecanoate) have been approved in the US only since 2019 but have obvious advantages in terms of ease of use and avoidance of a needle stick. However, bioavailability from oral formulations is far less than with injectables, and the pills must be taken with food in order for testosterone to be absorbed.

Alternatives to Testosterone

While treatment with testosterone itself is the most direct means of pharmacologically addressing low T, the decline in fertility that occurs with use of exogenous testosterone largely prohibits this approach in men who still plan to have children. In such cases, it is typically more desirable to use alternative therapies designed to raise *endogenous* testosterone – the testosterone produced “in-house” by the body. The two primary treatments for increasing endogenous testosterone production are clomifene (a.k.a. clomiphene; brand name Clomid®) and human chorionic gonadotropin (hCG).

Clomifene works by blocking the action of estradiol in the brain. Estradiol signaling inhibits the downstream production of pituitary hormones (specifically luteinizing hormone, or LH) responsible for driving the testicles to produce more testosterone (as well as more sperm), and therefore, interfering with estradiol’s action relieves this inhibition, leading to increased testosterone output. However, because the activity of estrogen is vital for sexual function and arousal, many patients find that clomifene results in a loss of libido. In contrast, hCG acts directly on the testicles by mimicking the action of LH, thus driving the production of testosterone and sperm without compromising sexual desire.

Though existing [evidence](#) indicates that TRT is likely the most potent means of raising testosterone levels, both [clomifene](#) and [hCG](#) have also been shown to be effective in this regard, as well as in promoting fertility. But unfortunately, not all patients with low T will see improvements on these TRT alternatives. Both treatments work by increasing the action of LH on the testicles, so both can correct for so-called “secondary hypogonadism,” in which dysfunction in the hypothalamic-pituitary axis results in low LH production and thus insufficient stimulation of the testicles. However, in cases of “primary hypogonadism,” the dysfunction is in the testicles themselves, as might result from various congenital conditions, chemotherapy or radiation of the area, or certain infections. In individuals with primary hypogonadism, clomifene or hCG will be ineffective, as the cause of low T is downstream of the actions of these drugs.

The bottom line

The TRAVERSE trial aimed to finally answer the question “Does TRT increase the risk of major cardiovascular events?” and settle the debate once and for all. Instead, this trial was more like a comparison between placebo and “placebo-plus,” essentially demonstrating the safety of increasing total serum T by small but probably not clinically relevant amounts. Although the paper concludes that TRT was not associated with any increase in CV events in men with established CVD or multiple cardiac risk factors, it is unclear if there would be a trend of increased events in this more vulnerable population if total and free T levels were increased in all men to the therapeutic range.

Given the significant effect that low T can have on the quality of life, the most prudent approach to prescribing TRT in higher-risk populations is to inform the patients of the possible risks and monitor known CV risk factors, including hematocrit and lipid levels and blood pressure, in addition to serum testosterone, especially over the first year of TRT. Despite the high hopes that the TRAVERSE trial would show the long-term safety and efficacy of TRT in men with higher CV risk, it would seem that we still don’t really have an answer for this subset of the population.

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