

# Impact of recent FDA ruling on testosterone replacement therapy (TRT)

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Submitted Aug 06, 2016. Accepted for publication Aug 08, 2016.

doi: 10.21037/tau.2016.09.08

View this article at: <http://dx.doi.org/10.21037/tau.2016.09.08>

## Introduction

Since its discovery in the 1930's, synthetic and bioidentical testosterone has been used to treat men with symptomatic hypogonadism. The growth of the pharmaceutical industry has evolved a range of options including oral, injectable, nasal bioadhesive and the particularly popular topical formulations.

Androgen use in US men  $\geq 40$  years old has more than tripled from 2001 to 2011 (1). The pharmaceutical industry, with aggressive direct to consumer marketing, touted TRT as the answer to decreased vitality, strength and libido. The "low T" disease awareness campaign contributed greatly to the number of middle-aged men getting tested for low testosterone and initiating TRT. On the [www.IsItLowT.com](http://www.IsItLowT.com) website, inactive since the 2015 U.S. Food and Drug Administration (FDA) ruling, men could take the Androgen Deficiency in Aging Males test. Additionally, they were counseled on how to broach the topic of low testosterone with their health care providers. The Endocrine Society has criticized these self-report quizzes for being unreliable and un-validated. It recommends against screening of otherwise healthy men for low testosterone (2,3).

The FDA has taken issue with the surge of the TRT industry for a variety of reasons. They have had to write several warning letters to many of the manufacturing companies expressing concern that promotional materials present misleading or unsubstantiated claims. It is worrisome that between 2001 and 2011, only 74.2% of those on TRT had testosterone levels measured in the previous year (1). Finally, results of cardiovascular (CV) studies questioning the safety of TRT have prompted FDA re-examination of current data.

In this article, we review FDA TRT regulation and the

ensuing public impact. We summarize the controversies surrounding the indications for therapy and the equipoise within the medical community as to the potential risks to CV health. We complete the report with the authors' thoughts on current evidence and the appropriate indications for TRT.

## The testosterone trials (T trials)

In 2003, the Institute of Medicine (IOM) concluded that available evidence did not unequivocally support the efficacy of TRT in men with low serum testosterone levels exhibiting symptoms of aging that may coincide with hypogonadism. The IOM called for research evaluating the efficacy of TRT in this population to definitively describe the benefits, if any. Reminiscent of the Women's Health Initiative, it suggested this research be conducted as coordinated trials. It especially noted that establishment of benefit must come before assessment of long term risk (4). Thus, the federally funded T trials were designed. The trials attempted to avoid the limitations of previous studies by use of a prospective design and enrollment of men with sufficiently low testosterone as to be unequivocally deficient. Also, candidate participants were objectively assessed for dysfunction. The hope was to evaluate the efficacy of TRT for 1 year in elderly men in seven domains: mobility, sexual function, fatigue, cognitive function, hemoglobin, bone density and coronary artery plaque volume. It is important to note that the trials were not powered such that conclusions about overall risk for CV events could be drawn (5). Results were not published until 2015.

Investigators noted high rates of comorbidities in the study population including obesity, hypertension and

history of CV disease. They concluded that TRT was successful in increasing moderately low serum testosterone levels in elderly men to the mid-normal range (for men aged 19–40 years). TRT treated participants reported a statistically significant increase in sexual desire and erectile function compared to the placebo cohort and a modest benefit in depressive symptoms. No clinically significant differences in vitality and walking distance were observed. However, treated men perceived an improvement in their walking ability and energy level compared to their baseline prior to TRT (6).

### Adult onset hypogonadism (AOH)

Araujo *et al.* applied the Endocrine Society's 2006 clinical practice guidelines to data from 1,475 men (mean age 47.3 years) in the Boston Area Community Health Survey. They concluded that most elderly men had testosterone levels in the normal range and many with low levels were asymptomatic. Their estimated crude prevalence of symptomatic deficiency was 5.6%, increasing with age (7).

The European Male Ageing Study (EMAS) was a prospective study of men aged 40 to 79 recruited from eight European centers. The investigators proposed that a diagnosis of late onset hypogonadism be based on a requirement of three sexual symptoms in addition to a total testosterone level <11 nmol/L and a free testosterone level <220 pmol/L. Seventeen percent of the EMAS sample had a testosterone level below 11 nm/L. A prevalence of 2.1% was observed with the proposed criteria, which increased with age, body mass index (BMI) and other comorbidities (8).

These studies have contributed to our current understanding of the distinct syndrome referred to as AOH. It is characterized by testosterone deficiency and low to normal gonadotropin levels due to hyposecretion of both the testis and pituitary. These men are unable to mount an adequate compensatory central response (9). This is in contrast to classical hypogonadism comprised of (I) primary hypogonadism with testicular dysfunction and (II) secondary hypogonadism due to central dysfunction. The Sexual Medicine Society of North America (SMSNA) recently acknowledged that 70% of men with AOH presenting with low gonadotropin levels have associated comorbid metabolic disease including diabetes, obesity and metabolic syndrome (9). This issue may be under-addressed in practice even though the Endocrine Society recommends screening diabetic men (3).

### Association between TRT and CV risks?

Before enrollment in T trials began, Basaria *et al.* sought to evaluate the efficacy of TRT on the physical function of elderly men with low testosterone levels in the Testosterone in Older Men with Mobility Limitations (TOM) trial. Although CV risk end points were not described in the study design, after enrollment of 209 patients the treatment group was found to have an increased rate of CV events compared to the placebo cohort. The study was discontinued prematurely. Of note, statistically significant improvements in leg and chest press strength, in addition to improvement in loaded stair climbing were observed in the treated group (10).

This question of whether or not exogenous androgen negatively impacts CV health prompted Vigen *et al.* to conduct a retrospective study assessing associations between TRT and all-cause mortality, MI or stroke. They concluded that in veterans with a history of coronary angiography and a documented testosterone level <300 ng/dL, TRT was associated significantly with adverse outcomes. The investigators noted that study limitations included possible variation in testosterone assays across hospitals and the fact that outcomes were not validated by chart review. Additionally, the time of day blood samples were drawn was unknown and testosterone levels are known to fluctuate diurnally (11).

Finkle *et al.* conducted a retrospective comparison of the incidence rates of MI 1 year before and 90 days after initiating TRT to the rates in a cohort of men prescribed specific phosphodiesterase type 5 (PDE5) inhibitors. They concluded that for those >65 years, the risk of MI in the 90 days after TRT initiation was twice that of the PDE5 inhibitor cohort. In men <65 years with a history of heart disease, a 2- to 3-fold increased risk was observed but there was no excess risk for those without this history. Limitations of the study included a lack of knowledge of the indications for TRT prescription within the cohorts, testosterone doses consumed and demographic data (12).

From a retrospective study of a sample of Medicare beneficiaries treated with intramuscular testosterone, Baillargeon *et al.* found no increased risk for hospitalizations for MI in the TRT cohort. They also found no dose response relationship between number of injections and MI hospitalization risk. In fact, a protective effect of TRT in those men with the highest MI prognostic index was observed. Limitations of the study included a lack of knowledge on use of other TRT formulations and inability

to assess medications that impact MI risk. Also, the baseline testosterone level of men in each cohort was unknown (13).

Shores *et al.* conducted a retrospective study of 1,031 veterans >40 years old (mean age 62.1 years) with a documented serum testosterone level  $\leq 250$  ng/dL. A lower testosterone threshold was utilized to increase the probability men had associated symptoms. A higher mortality rate was observed in those with lower baseline testosterone levels and those with a shorter duration of treatment. Overall, the mortality rate in the treated cohort was significantly lower than the untreated cohort. No significant effect modification by age, diabetes and CV disease was observed. Men <60 years old, diabetics and those without CV disease were found to have a greater mortality reduction with TRT. A major study limitation was the patient indication for TRT use was unknown to the investigators (14).

This handful of studies exemplifies the great degree of conflict in the current literature and has fueled the controversy with respect to the potential relationship between TRT and CV events. Current data does not definitively support a causal relationship for these adverse effects and prohibition of TRT on this basis is not warranted (15). However, the perspective to proceed cautiously in prescribing and monitoring is reasonable.

### **FDA 2015 ruling**

Androgen supplementation package inserts reference that TRT has been shown to decrease male fertility, increase hematocrit and induce hepatic dysfunction. Inserts also note that TRT may promote sodium and water retention resulting in edema (especially a concern for individuals with pre-existing congestive heart failure, renal and hepatic disease). Additional concerns include the potential for induction of gynecomastia, sleep apnea and hypercalcemia, changes in serum lipid profile, increased risk of venous thromboembolism and decreased thyroxine binding globulin. The FDA requires warning about the risk of worsening benign prostatic hyperplasia, a potential risk of prostate cancer and increase in prostatic specific antigen (PSA). How do clinicians interpret these? Are these legitimate concerns supported by the literature or are they hypotheticals? It is intuitive that testosterone would promote cancer recurrence in men with a history of the disease but several reports of off label use in this population do not reflect this. Regardless, TRT continues to be contraindicated in men with a history of prostate cancer.

On January 31, 2014, the FDA demanded a change in testosterone packaging to include a warning about the risks to CV health. Later that year, the Bone, Reproductive and Urologic Drugs Advisory Committee met to appraise the available data on the benefits and risks of TRT. This meeting employed presentations from a variety of stakeholders including the FDA, industry and community practice. During the meeting, the Endocrine Society testified that although testosterone use had increased, its use should be limited to men with documented consistently low serum testosterone levels with clinical manifestations of androgen deficiency. It further commented that testosterone levels are expected to decrease with aging and this decrease is not necessarily pathological. The society recommended more data be collected on various male populations to better determine which signs and symptoms and specific end organs benefitted from TRT (16). Thus the meeting closed with the FDA charging that further clinical research needed to be done by the TRT industry on the efficacy of the medication in the elderly population (results of the T trials had not yet been published). The FDA also limited the indicated population for TRT to those with "classical hypogonadism". In a March 2015 statement, the FDA specifically commented that they are aware of TRT being used to relieve symptoms of low testosterone of unknown etiology including aging but the benefits and safety of TRT in these men have not yet been established (17).

### **Public impact**

Public interest groups such as Public Citizen, petitioned the FDA to mandate a black box warning for the CV risk of testosterone. As the strongest prohibition the FDA can issue, the FDA rejected the petition citing a continued equivocal causal relationship between TRT and CV events.

Within 1 week of the FDA's 2014 announcement that it planned to re-examine the TRT efficacy and safety data, the first lawsuits were filed in Illinois against some of the manufacturers of topical formulations currently in use. Plaintiffs claimed that the CV risks of the drugs were withheld by the companies and they suffered debilitating MIs, strokes and clotting events as a result. These lawsuits were consolidated to be tried by a single judge in the United States District Court for the Northern District of Illinois. This was done in the interest of heightening efficiency, reducing costs incurred by both the plaintiffs and defendants and decreasing the potential for inconsistency

of ruling. Trials are expected to begin in October 2016 and continue into 2017.

It has yet to be seen what lasting effects the FDA regulation will have on United States testosterone sales. In 2006, Canadian policy changed such that on TRT prescriptions, prescribers had to specify documented low testosterone level and symptomatic central or testicular disease or a diagnosis of HIV for men  $\geq 65$  years. In the 9 years before this change, TRT prescriptions increased steadily. These did decline drastically the year of the policy change but returned to peak levels by 2012 when study observation ended (18).

### Professional response

Expectedly, the FDA ruling garnered the attention of the medical community as the majority of men who had previously enjoyed TRT as an option to alleviate a variety of symptoms that impacted their daily lives were now excluded. Several professional societies have released position statements and re-reviewed the available literature in response to the FDA ruling.

The American Urological Association (AUA) acknowledged that there is potential misuse of testosterone in areas such as performance enhancement and cautioned against use of over the counter preparations. The AUA noted that current evidence about the relationship between TRT and CV disease is equivocal; thus, frank discussions about the potential risks should be carried out between clinicians and hypogonadal patients. Eugonadal patients should not be offered this therapy. Unlike the FDA, the AUA believes TRT is appropriate for men with symptomatic hypogonadism which, may or may not be related to age. This view is shared by the SMSNA, the American Society for Men's Health and the Society for the Study of Male Reproduction (19).

The American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE) released a joint response. These groups highlighted that TRT has been associated with improvement in conditions associated with CV morbidity and mortality such as reducing fat mass and insulin resistance and increased lean muscle mass. The AACE and ACE also noted that the studies being referenced to show a negative relationship between TRT and CV health were either not designed to observe CV events having no specified criteria in study methodology or power to evaluate risk differences in these endpoints. Furthermore, retrospective analysis should serve

to guide hypothesis formation and is not a basis for drawing conclusions about clinical practice. Hypothesis testing should be accomplished with randomized prospective trials before conclusions can be drawn (20). Overall, the AACE and ACE do acknowledge that there are concerns that TRT could increase CV events, especially in those with pre-existing disease and that the benefits of TRT are most consistent in men with very low testosterone levels. Like the AUA, they support the use of TRT in symptomatic confirmed hypogonadal men regardless of etiology and patients should be counseled appropriately about the potential risks. However, they caution against its use in the frail elderly until more evidence of its safety in this population is ascertained.

### Authors' opinion

Diagnosis of hypogonadism should include both biochemical, confirmed by repeat morning testing, and clinical elements. While the threshold of 300 ng/dL is typically considered "unequivocally low" it is largely arbitrary. There are existing literature attempting to define a more robust threshold, but human variation is wide. Men have exhibited symptoms of hypogonadism at testosterone levels greater than 300 ng/dL; men have also remained completely asymptomatic at lower serum levels. The Endocrine Society recommends clinicians use their institutional laboratory's lower range of normal as their threshold. Furthermore, there is debate about which testosterone values should be evaluated: free or total? Are the requirements of older men the same as younger men, in whom the normal range was defined? Even our understanding of the clinical symptoms of hypogonadism and aging are evolving. The T trials attempted to clarify these relationships. Although this was somewhat successful, the symptoms of hypogonadism in the aging man remain unclear.

The IOM wanted an establishment of benefit and it would seem that TRT is beneficial, although perhaps not the fountain of youth desired as concluded by the T trials. With respect to a causal relationship between TRT and CV risk, there is still no answer. The T trials, like the studies before them, were not designed to shed light on this issue. The authors' opinion largely echoes that of the AUA: TRT should be available to all men with symptomatic low serum testosterone: both classical and AOH. While we respect the FDA's concerns, a broader population of men's needs should be recognized. Good clinical practice involves a

combination of clinical judgment, monitoring and honest conversations with patients about the potential benefits and risks of TRT based on current evidence.

The FDA recommended more robust randomized trials evaluating the efficacy and safety of TRT in various populations over the long term. We agree that these longitudinal studies may produce the answers we need to define the true CV risk but there are challenges. This ideal seems more of a lofty goal than a feasible objective. Such studies are costly in both time and effort and beg the question: who will finance and execute these endeavors? In the meantime, clinicians can only be expected to practice based on the data available.

## Conclusions

TRT has been available for decades but has been met recently with controversy. Attempts have been made by professional societies to understand the true indications for TRT; there is support for a biochemical and clinical diagnosis of hypogonadism. Moving forward, more trials are necessary to establish stronger evidence. The FDA desires increased rigor and follow up periods to provide answers, but there are many challenges to making these a reality.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Metzger SO, Burnett AL. Impact of recent FDA ruling on testosterone replacement therapy (TRT). *Transl Androl Urol* 2016;5(6):921-926. doi: 10.21037/tau.2016.09.08