Review Article

Testosterone therapy in the new era of Food and Drug Administration oversight

Bethany Desroches[1], Taylor P. Kohn[2], Charles Welliver[3], Alexander W. Pastuszak[1,4]

[1]Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA; [2]Baylor College of Medicine, Houston, TX, USA; [3]Department of Urology, Albany Medical College, Albany, NY, USA; [4]Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX, USA

Contributions: (I) Conception and design: AW Pastuszak, B Desroches, C Welliver; (II) Administrative support: AW Pastuszak, B Desroches, TP Kohn; (III) Provision of study materials or patients: B Desroches, TP Kohn, C Welliver, AW Pastuszak; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Alexander W. Pastuszak, MD, PhD. Assistant Professor, Division of Male Reproductive Medicine and Surgery, Center for Reproductive Medicine, Scott Department of Urology, Baylor College of Medicine, 6624 Fannin St, Suite 1700, Houston, Texas 77030, USA. Email: pastusza@bcm.edu.

Abstract: The Food and Drug Administration (FDA) introduced changes in labeling and indications for use to testosterone products in 2015 due to a possible increased risk of cardiovascular (CV) events. This decision was made based on six clinical studies—some that supported an increased CV risk, and some that did not. Since this decision, additional studies have been published examining the interplay between hypogonadism, CV risk, and testosterone, demonstrating that the risk may be lower than originally estimated. Clinicians are placed in a difficult position, as studies support an increased mortality risk in hypogonadal men, but also an increased risk of CV events in men on testosterone therapy. As a result, many clinicians will be more selective in their prescribing of testosterone. In this review, we examine how these new guidelines arose and how they may affect prescribing habits.

Keywords: Hypogonadism; low testosterone; cardiovascular risk; off-label use; practice patterns; physician's; drug prescriptions; united states food and drug administration

Submitted Mar 11, 2016. Accepted for publication Mar 11, 2016.
doi: 10.21037/tau.2016.03.13
View this article at: http://dx.doi.org/10.21037/tau.2016.03.13

Introduction

In March of 2015, the U.S. Food and Drug Administration (FDA) published a drug safety communication on the use of testosterone-containing products, warning patients and prescribers about the lack of consensus regarding a potential link between exogenous testosterone and the risk of cardiovascular (CV) events. As part of this communication, the FDA mandated new labeling of testosterone-containing products to highlight the potential increased risk of CV events, as well as to limit the approved indications for testosterone to hypogonadism of known etiologies, making the treatment of hypogonadism due to aging, as well as idiopathic hypogonadism, "off-label" (1).

The FDA panel's recent recommendations are likely to alter the way physicians prescribe testosterone and may influence how the general population views testosterone therapy (TTh). When deciding whether to prescribe testosterone, clinicians should be aware of the studies used by the FDA in making their recent recommendations, as well as other relevant studies prior to and after the FDA decision. In approaching patient care, it is important for clinicians to consider how TTh evolved to its present state and to anticipate how it will continue to change in the new era of increasing FDA oversight. In this review, we examine the work that led to the FDA panel decision, and the studies associating testosterone and CV risk performed since the panel's decision, in providing perspective on how management of hypogonadism is changing.

The 2014 FDA hearing—how did we get there?

Exogenous testosterone products have been FDA approved in the U.S. for over 50 years. However, there has been a dramatic increase in testosterone use in recent decades, and questions have arisen both about safety of these therapies as well as the direct-to-consumer marketing engaged in by pharmaceutical companies (2,3). The FDA recommendations and increased oversight are the culmination of multiple factors, with concerns about cardiovascular safety in men using the products serving as an obvious lightning rod for the FDA's involvement (1).

The FDA began investigating the potential increased CV risk associated with testosterone use in 2010 following the premature cessation of the Testosterone in Old Men (TOM) study—a randomized controlled trial that reported an increased risk of cardiac adverse events (4). The FDA performed a through review of the literature, yet found insufficient data supporting an association between CV risk and testosterone use at that time (3). In 2014, two observational studies that both suggested an increased CV risk in men who received testosterone prescriptions prompted the FDA to further evaluate the safety of testosterone (5,6). While multiple professional organizations have questioned the methods and quality of these studies, the majority of published data examining men on TTh is often comprised of short term studies that examine short-term effects on serum T levels, but were unable to evaluate long term safety outcomes (7).

While questions about CV safety appear to be the primary driver behind the FDA's March 2015 recommendation, a variety of other factors likely shaped the decision as well. As mentioned above, prescriptions for TTh have dramatically increased, and numerous factors have been cited as a cause of this increase, including increased direct-to-patient marketing by drug companies and questions about whether all the patients treated on testosterone should be receiving treatment (8,9).

Definitions and treatment of hypogonadism—are we treating a disease?

The FDA defines hypogonadism as a testosterone level ≤300 ng/dL, with no consideration for hypogonadal symptoms in that definition, and outlines the etiologies of hypogonadism for which testosterone therapy is merited. Of note, the recent FDA panel hearing resulted in exclusion of age-related and idiopathic hypogonadism from the list of indications for testosterone therapy (3).

Prior to the FDA ruling, testosterone prescriptions for age-related and idiopathic hypogonadism were abundant. From 2001 to 2011, a three-fold increase in testosterone prescriptions in the United States was observed, which coincided with increases in testosterone prescriptions in 37 of 41 countries studied worldwide (2,9). In the U.S., the most common reasons for prescribing testosterone were hypogonadism (51%), fatigue (34%), erectile dysfunction (ED) (32%), and psychosexual dysfunction (12%) (9). In a population that was living longer, age-related declines in serum testosterone levels were anticipated and treated. Both healthcare professionals and the public drove the increase in the treatment of what appeared to be a readily treatable syndrome. A study by Harman *et al.* in 2001 estimated that almost 20% of men over 60 years old and 50% of men over 80 years old had "hypogonadal" testosterone levels (10).

One of the questions evaluated by the FDA during the 2014 hearing was whether age-related decreases in serum testosterone levels represented a disease that merited treatment. Numerous professional societies have recommended that the FDA's definition of hypogonadism be adjusted to include symptoms such as such as decreased libido, erectile dysfunction, depression, and fatigue as well as age-appropriate testosterone levels given the aging population and the associated age-related declines in testosterone (11). For example, the Endocrine Society defines hypogonadism as the presence of both low testosterone levels and hypogonadal symptoms, and concludes that it may be the combination of symptoms and serum testosterone levels that benefits from treatment (12).

Several studies have investigated how aging impacts both symptomatic and asymptomatic testosterone deficiency. In 2010, the European Male Aging Study (EMAS) prospectively examined 3,369 men 40–79 years old and specifically defined late onset hypogonadism (LOH) as the presence of three sexual symptoms (decreased frequency of morning erections and sexual thoughts, and erectile dysfunction) as well as a testosterone level <320 ng/dL (13,14). Using these strict criteria, only 5.1% of men over 70 years old fit the definition of LOH, in contrast with 17% of all men in the cohort when using only a testosterone threshold to define LOH. A smaller retrospective study demonstrated that men <40 years old develop hypogonadal symptoms at a serum testosterone level closer to 400 ng/dL, further supporting age-related differences in serum testosterone levels resulting in symptomatic hypogonadism (15). The Boston Area Community Health (BACH) Survey applied the Endocrine Society definition of hypogonadism to 1,475 men and found

an increasing prevalence of hypogonadism, from 3% in men 30–39 years old to 18.4% of men over 70 years old (16). These studies helped to more strictly define hypogonadism and its prevalence, but could not define the relationship between hypogonadal symptoms and TTh.

Associations between hypogonadism and men's health

By 2015, the use of TTh had markedly increased. However, a significant proportion of men receiving testosterone were incompletely evaluated prior to initiating therapy (3). In 2007, Katz *et al*. observed that of 902 men who were given new testosterone prescriptions, only 17% had serum testosterone levels checked (17). In 2013, Baillargeon *et al*. published that among all new testosterone users, only 75% had testosterone levels measured in the 12 months prior to receiving a testosterone prescription (9). This was of obvious concern, as it appeared that testosterone was being used as a modern panacea for men's ailments, and physicians were failing to perform basic diagnostic testing before prescribing treatment. This observation likely increased scrutiny on testosterone prescribing, particularly in the absence of clear data at the time linking improvement in hypogonadal symptoms with other conditions associated with hypogonadism in older men treated with TTh. In the absence of strong data that linked amelioration of hypogonadism and its associated risks, particularly in older men, with safe administration of TTh, the FDA believed that stricter guidelines were indicated to narrow the subpopulations of men that received testosterone safely (3).

Numerous conditions are associated with hypogonadism, including obesity, metabolic syndrome, and diabetes mellitus. The NIH estimates that almost 3 in 4 men (74%) are overweight or obese, and approximately 45% of obese men are also hypogonadal (18,19). Endogenous testosterone levels are inversely related to body mass index (20). Hypogonadism is also associated with diabetes, even in non-obese patients (21). It is also associated with hyperlipidemia, thyroiditis, chronic obstructive pulmonary disease (COPD), and even vitamin D deficiency (22). These studies show a correlation between illnesses and low testosterone, which prompts the question: is androgen deficiency a marker of declining health?

Many of these conditions can be improved with TTh. A recent paper by Dhindsa *et al*. found that testosterone therapy in hypogonadal men with type 2 diabetes improved insulin sensitivity and decreased subcutaneous fat (23). TTh has also consistently been shown in randomized controlled trials to improve quality of life and sexual function (24-26). Finally, two of the adverse effects long associated with TTh, prostate cancer and lower urinary tract symptoms, have recently been shown in meta-analyses to be insignificantly impacted by TTh (27,28).

The population of men presenting with hypogonadism have twice the mortality risk when compared to men with normal testosterone levels (29,30). In one study examining men admitted to the hospital with acute myocardial infarction, low testosterone levels on admission were independently related to higher mortality after 30 days (31). If the underlying comorbidities that predispose to hypogonadism and its associated symptoms are not treated, and instead the patient is merely treated with TTh to address his hypogonadism, it follows that the patient's risk of a future morbidity and mortality may increase.

Cardiovascular risks

The FDA panel evaluated studies examining the relationship between TTh and cardiovascular events, and identified six studies with conflicting results for consideration by the panel (3). While the FDA concluded that more research was needed to definitively determine the relationship between CV events and testosterone, they also found a weak signal supporting a relationship meriting a change in testosterone labeling warning about a possible increased CV risk in patients using testosterone.

In 2010, Basaria *et al*. published their data on 209 men, all over 65 years old, with pre-treatment testosterone levels between 100–300 ng/dL (4). Of these men, 50% had known cardiac disease. The subjects were randomized to placebo versus 10 grams topical testosterone gel treatment, with a primary endpoint of leg press muscle strength. The study found a significant improvement in muscle strength, but the trial was stopped early because of a significantly higher incidence of CV events, including cardiac events, need for stents, arrhythmias, and hypertension, in the testosterone group. These CV events occurred more frequently in men with testosterone levels of 500–1,000 ng/dL (24%) and >1,000 ng/dL (29%). In contrast, in men whose testosterone levels remained <500 ng/dL, only 15% experienced CV-related events. As a result of these findings, the trial was stopped early and spurred work in the following years to investigate the cardiac risks of TTh.

The next study included in the FDA analysis was an observational, retrospective trial by Vigen *et al*. evaluating 8,709 hypogonadal men who had undergone cardiac

catheterization (5). In this trial, the authors compared men who were prescribed testosterone after their catheterization versus men who never were given testosterone. Men who had received testosterone had an increased risk of mortality, myocardial infarction, and ischemic stroke. Another study that reported an increased risk of CV events was performed by Finkle *et al*. in 2014. This retrospective cohort study looked at first time non-fatal myocardial infarctions in men on testosterone compared to men on PDE5 inhibitors, and found that older men without prior CV disease who had filled a prescription for TTh were at 1.36-fold increased risk of myocardial infarction when compared to men who had not filled a testosterone prescription (6).

Two studies included in the FDA's review observed increased mortality in hypogonadal men who were not on TTh. The first of these studies was done by Shores *et al*. in 2012, who demonstrated in a retrospective cohort of 398 men that hypogonadal men treated with testosterone had significantly decreased risk of mortality when compared to hypogonadal men who did not receive TTh (HR =0.61) (32). The second study, by Muraleedharan *et al*., demonstrated an increased risk of mortality in hypogonadal men (29). This retrospective cohort study of 236 hypogonadal men with type II diabetes found that men not receiving TTh had a 2-fold increased risk of all-cause mortality when compared to men on TTh.

The final study that the FDA considered in its decision was published by Baillargeon *et al*. in 2014 (33). This retrospective analysis of 6,355 men found no significantly increased risk of myocardial infarctions in hypogonadal men who received at least one injection of testosterone compared to hypogonadal men who had not received TTh. When this population was sub-analyzed, it was found that testosterone was modestly protective for men who were at high risk of myocardial infarction. While both physicians and patients will benefit from additional clinical trials to delineate the possible association of TTh and CV risk, and several of these have already borne fruit since the FDA ruling, the FDA's decision was nevertheless based on only these few studies.

Treatment of hypogonadism after the FDA ruling—what's do we know now?

Since the FDA ruling in March 2015, a variety of new studies looking at the safety of TTh have been published. The most compelling of these is a randomized placebo-controlled trial of over 700 men who were followed for one year. While the clinical trial outcomes described in this paper primarily focused on improvements in either sexual function, physical function or vitality resulting from TTh, no difference in cardiac events was observed when comparing TTh to placebo (34). However, the study was not powered to evaluate this endpoint.

Another retrospective study by Sharma and colleagues assessed over 83,000 male veterans, examining cardiac outcomes in men with untreated low T levels (group 3), incompletely treated low T levels (on treatment but below-normal serum testosterone levels) (group 2), and men who reached normal testosterone levels with treatment (group 1). The authors found that all-cause mortality, stroke, and risk of myocardial infarction were lower in group 1 compared to group 3. These differences were also seen between group 1 and group 2, potentially demonstrating a benefit to ensuring adequate and complete return of eugonadism in men. There was no difference in stroke risk or MI in men who were in group 2 and group 3 (35).

Off-label testosterone therapy—prescribing practices after the FDA ruling

The change in indications for treatment of hypogonadism has made the treatment of aging-related, idiopathic and metabolic hypogonadism "off-label." If a physician chooses to use testosterone outside the FDA-approved labeling, they must be well informed about the risks and benefits of the product, use appropriate judgment, employ evidence-based medicine, and maintain records of the decision. This modification to how hypogonadism is defined is likely to lead to two competing results: (I) the FDA panel ruling may change the way some physicians view hypogonadism in their patients, with some physicians treating only hypogonadism with a discrete and clinically established etiology; or (II) physicians may continue to treat hypogonadism as they have, writing more off-label prescriptions, without the expectation of drug coverage by insurance companies. This latter result may lead patients on routine TTh to utilize compounding pharmacies which increasingly produce these medications at an affordable price point for patients.

Will the number of prescriptions of testosterone decrease overall based on diminishing insurance coverage? A 2014 Canadian study by Piszczek *et al*. studied a group of men whose insurance no longer covered their preferred form of testosterone treatment. Over the short term, testosterone prescribing declined 27.9%. However, after six months, testosterone use exceeded pre-policy levels (36). With the change in FDA recommendations, the use of

compounding pharmacies and out-of-pocket payment for treatment of this diagnosis may increase. The patient population may be willing to pay directly for a medication that ameliorates their symptoms, and a competitive market will drive prices down. As more patients resort to compounding pharmacies and compounding pharmacy industry grows by a projected 3.5% from 2015 to 2019, the cost of equivalent medicines approximates the co-pay of the originally prescribed testosterone therapy and thus does not serve to discourage motivated patients from obtaining the medications that may impact their quality of life (37).

Summary

In 2015, the FDA found a "weak signal" in the literature supporting an increased CV risk associated with TTh. While the medical community continues to debate this relationship, recent FDA recommendations serve to better inform men of potential health risks associated with TTh. The FDA's decision was made in the face of rising numbers of testosterone prescriptions and in the absence of high quality data demonstrating safety and efficacy of TTh in the treatment of hypogonadism, particularly in older men. The repercussions of the FDA's decision remain to be truly felt, and future work will determine if the FDA's decision results in optimal patient treatment. High quality randomized controlled trials and decisive meta-analyses are needed to determine if the purported CV risk associated with testosterone is truly present. Until that day, clinicians must be selective in their prescribing of TTh in this new era of FDA oversight.

Acknowledgements

Funding: AW Pastuszak is a National Institutes of Health (NIH) K12 Scholar supported by a Male Reproductive Health Research Career (MHRH) Development Physician-Scientist Award (HD073917-01) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Program (to Dolores J. Lamb).

Footnote

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

References

1. Research CfDEa. Drug Safety and Availability - FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use.
2. Handelsman DJ. Irrational Exuberance in Testosterone Prescribing: When Will the Bubble Burst? Med Care 2015;53:743-5.
3. Research CfDEa. Bone, Reproductive and Urologic Drugs Advisory Committee - Slides for the June 4, 2015: Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting.
4. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109-22.
5. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829-36.
6. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014;9:e85805.
7. Group TAS. Twenty-Five Medical Societies Join Androgen Study Group to Petition JAMA to Retract Misleading Testosterone Study. 2014.
8. Nguyen CP, Hirsch MS, Moeny D, et al. Testosterone and "Age-Related Hypogonadism"--FDA Concerns. N Engl J Med 2015;373:689-91.
9. Baillargeon J, Urban RJ, Ottenbacher KJ, et al. Trends in androgen prescribing in the United States, 2001 to 2011. JAMA Intern Med 2013;173:1465-6.
10. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724-31.
11. Schubert M, Jockenhövel F. Late-onset hypogonadism in the aging male (LOH): definition, diagnostic and clinical aspects. J Endocrinol Invest 2005;28:23-7.
12. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536-59.
13. Lee DM, Pye SR, Tajar A, et al. Cohort profile: the European Male Ageing Study. Int J Epidemiol 2013;42:391-401.
14. Pye SR, Huhtaniemi IT, Finn JD, et al. Late-onset hypogonadism and mortality in aging men. J Clin

Endocrinol Metab 2014;99:1357-66.
15. Scovell JM, Ramasamy R, Wilken N, et al. Hypogonadal symptoms in young men are associated with a serum total testosterone threshold of 400 ng/dL. BJU Int 2015;116:142-6.
16. McKinlay JB, Link CL. Measuring the urologic iceberg: design and implementation of the Boston Area Community Health (BACH) Survey. Eur Urol 2007;52:389-96.
17. Katz A, Katz A, Burchill C. Androgen therapy: testing before prescribing and monitoring during therapy. Can Fam Physician 2007;53:1936-42.
18. Ogden CL, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA 2012;307:483-90.
19. Calderón B, Gómez-Martín JM, Vega-Piñero B, et al. Prevalence of male secondary hypogonadism in moderate to severe obesity and its relationship with insulin resistance and excess body weight. Andrology 2016;4:62-7.
20. Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation 2007;116:2694-701.
21. Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care 2010;33:1186-92.
22. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male 2015;18:5-15.
23. Dhindsa S, Ghanim H, Batra M, et al. Insulin Resistance and Inflammation in Hypogonadotropic Hypogonadism and Their Reduction After Testosterone Replacement in Men With Type 2 Diabetes. Diabetes Care 2016;39:82-91.
24. Ho CC, Tong SF, Low WY, et al. A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. BJU Int 2012;110:260-5.
25. Hackett G, Cole N, Bhartia M, et al. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. J Sex Med 2013;10:1612-27.
26. Tong SF, Ng CJ, Lee BC, et al. Effect of long-acting testosterone undecanoate treatment on quality of life in men with testosterone deficiency syndrome: a double blind randomized controlled trial. Asian J Androl 2012;14:604-11.
27. Boyle P, Koechlin A, Bota M, et al. Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate specific antigen (PSA): a meta-analysis. BJU Int 2016. [Epub ahead of print].
28. Kohn TP, Mata DA, Ramasamy R, et al. Effects of Testosterone Replacement Therapy on Lower Urinary Tract Symptoms: A Systematic Review and Meta-analysis. Eur Urol 2016. [Epub ahead of print].
29. Muraleedharan V, Marsh H, Kapoor D, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013;169:725-33.
30. Shores MM, Matsumoto AM, Sloan KL, et al. Low serum testosterone and mortality in male veterans. Arch Intern Med 2006;166:1660-5.
31. Militaru C, Donoiu I, Dracea O, et al. Serum testosterone and short-term mortality in men with acute myocardial infarction. Cardiol J 2010;17:249-53.
32. Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012;97:2050-8.
33. Baillargeon J, Urban RJ, Kuo YF, et al. Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy. Ann Pharmacother 2014;48:1138-44.
34. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of Testosterone Treatment in Older Men. N Engl J Med 2016;374:611-24.
35. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015;36:2706-15.
36. Piszczek J, Mamdani M, Antoniou T, et al. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. PLoS One 2014;9:e98003.
37. IBISWorld. Compounding Pharmacies in the US: Market Research Report.

Cite this article as: Desroches B, Kohn TP, Welliver C, Pastuszak AW. Testosterone therapy in the new era of Food and Drug Administration oversight. Transl Androl Urol 2016;5(2):207-212. doi: 10.21037/tau.2016.03.13

