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UNSOLICITED REVIEW

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The state of testosterone therapy since the FDA's 2015 labelling changes: Indications and cardiovascular risk

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Summary

Objective: A label change in testosterone (T) products in March 2015 followed a highly publicized FDA advisory committee meeting in September 2014. Changes included a warning of possible increased cardiovascular (CV) risks and restriction of indicated populations to younger men with a limited set of known aetiologies of testosterone deficiency (TD). These changes greatly impacted clinical practice and public perception of T therapy (TTh). Our aim was to review these changes in the light of subsequently published studies.

Design: We identified 23 studies through June 2017, including 12 clinical trials and 11 observational studies. The Testosterone Trials included 790 men aged 65 years and older with TD without known aetiology, assigned to 1-year T gel or placebo.

Results: Demonstrated benefits of T included sexual activity and desire, physical activity and mood. There were 9 major adverse CV events (MACE) in the T arm and 16 in the placebo arm. No study reported increased MACE with TTh. A 3-year RCT showed no difference in carotid atherosclerosis. Several large observational studies reported reduced CV events with TTh, including one showing progressively reduced CV and mortality risk with greater duration of TTh. Men whose serum T normalized with TTh had reduced risk of MI and death compared with men whose T levels failed to normalize.

Conclusion: We conclude that existing evidence fails to support increased CV risk with TTh; on the contrary, there is evidence suggestive of real-world CV benefits. Finally, existing evidence provides benefits of TTh in older men without known aetiology for T deficiency.

KEYWORDS

Cardiovascular Disease, FDA Labelling, Food & Drug Administration, Testosterone, Testosterone Deficiency

1 | INTRODUCTION

In January 2014, the FDA announced it would convene an advisory committee meeting to review cardiovascular (CV) risks of testosterone (T) therapy (TTh), shortly after publication of two observational studies that reported increased CV risks with TTh.[1,2] Several months later, the FDA expanded the stated purpose of the advisory committee meeting to include a review of the suitable populations for TTh.[3] On 17 September 2014, the advisory committee voted 20-1 to restrict the indicated population for TTh and require the pharmaceutical companies to perform a cardiovascular safety study.

In March 2015, all US commercial T products underwent an FDA-mandated label change that: (i) restricted the indicated population and (ii) warned against the possible risk of myocardial infarction and stroke.[4] Authors from the responsible FDA team subsequently published their rationale and perspective in a leading medical journal

in August 2015.[5] Other regulatory bodies, including the European Union and Health Canada, have also issued warnings regarding TTh and potential cardiovascular risk. A review by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommended updating the product information warning about the potential increased CV risk in hypogonadal men using TTh. In addition, Health Canada also issued warnings to consumers and healthcare providers about a potential CV risk linked to TTh.

These actions by the FDA were extensively covered by the lay and medical media and contributed to concerns that TTh is associated with previously under-recognized risks and is overprescribed. The label change regarding indicated populations created an unusual situation in which TTh prescriptions for a large majority of men with well-recognized condition of T deficiency (TD) also, known as adult-onset hypogonadism[6] suddenly became "off-label" overnight, adding to the concern that physicians are prescribing T for no reason other than normal ageing. The added CV warning has caused physicians to discuss this speculative risk with all new candidates for TTh. Our experience with colleagues and referring healthcare providers is that these changes have reduced the willingness of many professionals to consider treatment for affected men with TD. In addition, health insurers have created policies based on these changes to justify reduced coverage for T products.

In the light of these major changes to the field, we believe there is considerable value in reviewing the evidence leading to these changes, and whether subsequently published studies support such changes. We here review these studies with an eye towards CV risk and indicated populations to arrive at an evidence-based assessment of the current state of TTh.

2 | CHANGES TO THE FDA LABEL

Although the addition of a CV warning to the label for TTh products received considerable attention, it should be noted that warnings of this type are not uncommon. In fact, there were already 15 existing warnings for AndroGel, the leading T product, prior to the addition of the CV warning, covering items such as secondary exposure to women and children, hepatic toxicity, oedema, gynaecomastia and polycythaemia. Not all of these warnings are supported by evidence in the literature. For example, many studies show no effect or benefits of TTh for lower urinary tract symptoms,[7,8] despite a warning that symptoms of benign prostatic hyperplasia may worsen with treatment.

Moreover, the language contained in the warning is not particularly alarming. It reads as follows: "Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction (MI), non-fatal stroke, and cardiovascular (CV) death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men."

In addition, the language for indications was changed by the FDA to provide an inclusive list of conditions causing hypogonadism, termed "classical hypogonadism," and removing the term "idiopathic," which accounted for a large majority of treated cases prior to the issuing of the warning. Finally, a statement was added as follows: "Safety and efficacy of AndroGel 1.62% in men with 'age-related hypogonadism' (also referred to as 'late-onset hypogonadism') have not been established."

Below, we review the relevant literature that addresses these issues of CV risk and new restrictions for indicated therapeutic use.

3 | STATUS OF PUBLISHED STUDIES LEADING TO ADDITION OF CV RISK WARNING

We have previously published a comprehensive review of the relevant CV literature prior to the FDA advisory committee meeting.[9] Briefly, the FDA pharmacovigilance team identified only four studies suggesting increased CV risks with T therapy. The first, in 2010, was a 6-month placebo-controlled T gel study in frail men, with limited mobility, in which more CV events were noted in the T arm compared with the placebo arm.[10] However, a majority of these events were not clinically significant and included nonspecific changes in electrocardiogram, palpitations and pedal oedema not associated with heart failure. It has been suggested that some of these events were associated with higher serum concentrations of T achieved with treatment using higher than approved doses of T.[9,10] The authors of the study also stated that differences between the two groups may be attributed to chance.[10] The FDA's own written assessment indicated they dismissed these results as concerning because the numbers of major adverse cardiovascular events (MACE) were too few for evaluation.[11]

The second by Vigen et al[1] was an observational study of 8507 men in the Veteran's Administration health system who underwent cardiac angiography and had low serum T concentrations. It was reported that men who subsequently received TTh had an absolute rate of MI, stroke or death of 25.7% at 3 years following angiography compared with 19.9% in untreated men. Soon after publication it was discovered the authors had reversed their results, as the absolute rate of events was only 10.1% among men who received TTh and 21.2% in untreated men. Later, the authors revealed they had miscategorized over 1000 individuals in the original publication, and nearly 10% of the all-male population was discovered to be women. More than 165 leading researchers and 29 medical societies called for retraction of the study[12]; however, it remains extant.

A third study by Finkle et al[2] reported increased rates of nonfatal MI in the 90 days following a T prescription compared with the prior 12 months. Apart from serious methodological concerns (the period prior to the prescription represents physician prescribing

behaviour rather than a natural rate of MI), there was no control group of hypogonadal men who did not receive a T prescription, so it is unknown whether rates of MI were higher, lower or unchanged in this population. Finally, one meta-analysis of placebo-controlled T trials reported increased CV events for men who received T.[13] However, as the FDA noted, this study's results were confounded by incorrect data culled from the component studies and an overly broad definition of what constituted a CV event. The FDA's own analysis indicated that the number of important CV events was similar in the T- and placebo-treated groups.[11] At least 6 other meta-analyses found contradictory results, with no increased T-associated CV risks.[14-19] The largest of these suggested decreased risks of men at high CV risk due to cardiometabolic disorders.[14]

In contrast, there is a substantial literature indicating that low T levels are associated with increased mortality, coronary artery disease (severity and incidence), increased fat mass, and decreased lean mass.[9] Two observational studies reported reduced mortality, by half, in men with low T who received TTh compared with untreated men.[20,21] And several small- to moderate-sized placebo-controlled trials showed CV benefits with T administration in men with known CV disease, specifically angina and heart failure.[22-27]

While the new FDA warning is accurate in that some studies did report increased CV risks with T administration whereas others did not, the strength of the few studies suggesting any increased risk was remarkably weak. It is noteworthy that the European Medicines Agency performed its own review and declined to add a new CV warning.[28]

4 | REVIEW OF NEW CV STUDIES

Since the FDA advisory committee meeting in September 2014, 23 new studies published addressing CV risks of TTh. This includes 12 clinical trials[29-40] and 11 observational data analyses.[41-51] Five of these studies comprise the T Trials.[29-34] These clinical and observational trials are briefly reviewed here. Studies were identified via a search of the US National Library of Medicine with keywords testosterone and cardiovascular, and for published studies from 1 September 2014 through June 2017 inclusively. Studies that failed to include relevant CV outcomes were excluded.

4.1 | Controlled trials

In February 2016, the first results of the Testosterone Trials were published[29] followed by several publications through mid-2017. This was arguably the most important T trial to date, representing the first large, government-funded, multicentre, placebo-controlled trial involving 790 men 65 years or greater assigned to either T gel or placebo for 1 year. The trial included a second year to monitor for safety outcomes. The T Trials confirmed what clinicians have known for decades—TTh improved sexual function, sexual desire (increase in testosterone levels was associated with significantly increased sexual activity, as assessed by the Psychosexual Daily Questionnaire ($P < .001$), as well as significantly increased sexual desire and erectile function), physical activity (the percentage of men who had an increase of at least 50 m in the 6-minute walking distance did not differ significantly between the two study groups in the Physical Function Trial but did differ significantly when men in all three trials were included [20.5% of men who received testosterone vs 12.6% of men who received placebo] ($P = .003$) and mood. Rates of MACE were identical in the first year for the T and placebo arms, with N = 7. However, in the second year there were only 2 major cardiovascular events (MACE) in the T arm compared with 9 in the placebo arm, albeit not statistically significant. Hospitalizations and deaths were greater in the placebo arm. It is important to recognize that this study is not powered to draw conclusions regarding the safety profile of T products.

Subsequently, Budoff et al[34] presented results of CT angiography in a subset of 138 men from the T Trials. Compared with placebo, TTh was associated with a significantly greater increase in noncalcified and total plaque volume, but not in calcified plaque. No major cardiovascular events occurred in either treatment group. Although these results would appear concerning, it is difficult to conclude that this study demonstrated increased CV risk. First, the volume of noncalcified plaque has not been associated with CV outcomes, so the significance of this finding is unknown.[52] Second, coronary calcium scores do have a well-established association with CV outcomes, and this measure did not change with T administration.[53] Finally, there were no adverse CV events in this subgroup, and as noted above, for the entire study population of 790 men in the T trials there were a greater number of MACE in the placebo arm than the T arm (16 vs 9, respectively).

Noncalcified plaque volumes increased in the T arm from 204 to 232 mm^3 compared with 317 to 325 mm^3 in the placebo arm (estimated difference 41 mm^3; 95% CI, 14 to 67 mm^3; $P = .003$). Although the increase was greater in the T arm, the placebo group had a greater burden of noncalcified plaque by 55% at baseline and 40% at the end of 12 months. This difference between groups is larger than the observed changes over time for either group, indicating the two treatment arm populations were substantially different at baseline. This makes it impossible to know whether the observed results were due to baseline population differences or the drug intervention.

A randomized placebo-controlled study by Dhindsa et al[40] evaluated the effects of insulin resistance in men with type 2 diabetes and hypogonadotrophic hypogonadism. A total of 94 diabetic men were evaluated of which 50 men were eugonadal and 44 men were hypogonadal. Hypogonadal men were randomized to receive 250 mg intramuscular testosterone or placebo every 2 weeks for 24 weeks. Insulin sensitivity was calculated from the glucose infusion rate (GIR) during hyperinsulinaemic-euglycaemic clamp. Lean body mass and fat mass were also assessed. These authors found after 24 weeks that GIR significantly increased by 32% in the TTh group and did not change in the placebo group ($P = .03$). TTh also resulted in a significant improvement in fat mass (−3.3 kg) and lean body mass (+3.4 kg) over placebo ($P < .01$).[40]

In another small RCT to evaluate the efficacy of TTh on pain perception and other androgen-dependent outcomes in men with opioid-induced androgen deficiency, Basaria et al[36] randomized 84 participants (ages 18-65 years with T levels <350 ng/dL) taking opioid analgesics for noncancer pain to 5 g testosterone gel or placebo for 14-week duration. Compared with men assigned to the placebo arm, those assigned to TTh experienced greater improvements in pressure and mechanical hyperalgesia, sexual desire and role limitation due to emotional problems. In conclusion, in men with opioid-induced androgen deficiency, T administration improved pain sensitivity, sexual desire, body composition and aspects of quality of life with no major adverse cardiovascular events in either group.

In 2015, investigators participated in a long-term study of 334 patients older than 40 years in Japan. This was a randomized controlled trial to examine the effect of TTh (T enanthate vs placebo) on the condition of late-onset hypogonadism (LOH).[37] These men had decreased T levels of advancing age together with appropriate clinical signs and symptoms to meet the criteria for treatment of LOH according to multiple society definitions. Fifty-two weeks after the initial treatment, TTh significantly affected the physical subdomain of the short form-36 health survey (SF-36) scale ($P = .0318$) in a positive fashion, was associated with significant decreases in waist circumstance ($P = .002$) and serum triglycerides ($P = .013$), and was associated also with significant increases in whole-body and leg muscle mass volumes ($P = .071$ and 0.0108, respectively), serum haemoglobin ($P < .001$), IPSS voiding subscore ($P = .0418$) and the second question on IIEF-5 ($P = .0049$) (improved voiding and sexual function). There was no significant difference between the groups in terms of severe adverse events. Lastly, Paduch et al[38] investigated the effect of the application of a 2% testosterone solution on the axillae of 76 T-deficient participants in a randomized controlled trial to determine the impact of testosterone therapy on ejaculatory dysfunction (delayed ejaculation, anejaculation, reduced ejaculate volume and/or reduced force of ejaculation) in testosterone-deficient men. TTh over 16 weeks improved the MSHQ-EjD-SF score (mean score change, +3.1); however, this effect was not statistically different from placebo (mean score change, +2.5; $P = .596$) and the study concluded T had no impact on ejaculatory or orgasmic function in T-deficient men. Once again, no adverse cardiovascular effects were detected in either group.

Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) was a 3-year placebo-controlled, double-blind, parallel-group randomized trial involving 308 men aged 60 years or older with low or low-normal T levels (100-400 ng/dL; free T < 50 pg/mL).[39] One hundred and fifty-six participants were randomized to receive 7.5 g of 1% T, and 152 were randomized to receive placebo gel packets daily for 3 years, with dose adjustment targeted to achieve T levels between 500 and 900 ng/dL. Coprimary outcomes included common carotid artery intima-media thickness and coronary artery calcium; secondary outcomes included sexual function and health-related quality of life. Results were that T administration for 3 years vs placebo did not result in a significant difference in the rates of change in either common carotid artery intima-media thickness or coronary artery calcium. No MACE were reported because this trial was only powered to evaluate atherosclerosis progression, and therefore, these findings should not be interpreted as establishing cardiovascular safety of testosterone use in older men. However, the lack of CVD events is reassuring that testosterone therapy did not cause serious mortality or morbidity.

4.2 | Observational studies

In 2015, Etminan et al[41] performed a case-control study within a cohort of 934 283 men aged 45-80 from a large Health Plan Claims Database. For each case of MI, four controls were identified using density-based sampling. The mean age for the cases and controls was 70.4 (±13) years with a mean follow-up of 2.8 (±2.2) years. Cases were more likely to have been previously diagnosed with stroke, peripheral vascular disease, cancer or chronic renal failure than controls. Rate ratios (RRs) were computed for current and past TTh users. As a sensitivity analysis, the risk of MI before and after the start of a first-time TRT prescription in the same patient was also computed. One limitation of cohort studies of treatment constructed by record linkage is that they are vulnerable to time-related biases.

The investigators identified 30 066 MI cases and 120 264 corresponding controls. Current use of TRT was not associated with an increased risk of MI (RR 1.01, 95% confidence interval [CI] 0.89-1.16); first-time users did show an increased risk (RR 1.41, 95% CI 1.06-1.87 with a number needed to harm of 305; this was deemed a relatively small absolute risk by the investigators). These results should be viewed in the light of evidence suggesting the condition of T deficiency may itself confer increased risk of CV events. There was no association between MI and past TRT users and no differences among the different formulations. The RRs for current use and first-time use of TRT in men with a previous history of coronary artery disease were 1.05 (95% CI 0.79-1.41) and 1.78 (95% CI 0.93-3.40), respectively, and not clinically significant.

The study has several strengths. First, due to the large sample size, it includes the largest number of cases of MI with TRT exposure (n = 515). Second, analyses controlled for the most common potential confounders and examined the time dependency of TRT risk patterns. Third, before and after sensitivity analyses effectively removed between-subject variability. Lastly, the study had adequate statistical power to potentially show an increase in the risk of MI, if it existed.

Wallis et al[42] reported on a population-based matched cohort study of men aged 66 years or older treated with T and controls matched for age, region of residence, comorbidity and diabetes status. The study included 10 311 men treated with T and 28 029 untreated with a median follow-up of 5.3 years in the T group and 5.1 years in the control group. Overall, men in the T group had lower mortality than did controls (hazard ratio [HR] 0.88, 95% CI 0.84-0.93). Interestingly, greater duration of treatment was associated

with greater reduction in risk. Patients with the shortest duration tertile of T exposure had an increased risk of mortality (HR 1.11, 95% CI 1.03-1.20) and CVD events (HR 1.26, 95% CI 1.09-1.46) compared with controls. In contrast, those in the highest tertile of T exposure had decreased risk of mortality (HR 0.67, 95% CI 0.62-0.73) and CVD events (HR 0.84, 95% CI 0.72-0.98).

Sharma et al[43] retrospectively examined national data on 83 010 men with documented low testosterone, all age 50 or above, who received care from the Veteran's Administration between 1999 and 2014, the largest and longest observational study to date. Men were divided into three groups: (i) 43 931 men whose serum T normalized with T therapy, (ii) 25 701 men whose serum T failed to normalize despite T therapy and (iii) 13 378 untreated men with low T concentrations. Groups were matched for age, body mass index, various chronic diseases, LDL cholesterol levels and medications. The average follow-up was 4.6 to 6.2 years. Compared with untreated men, treated subjects with normalized T were 56% less likely to die during the follow-up period ($P < .001$), 24% less likely to suffer an MI ($P = .005$) and 36% less likely to have a stroke ($P = .031$). Similar results were observed for treated men with normalized T compared with treated men without T normalization. Normalization was associated with 37% reduction in death ($P < .001$), 18% reduction in MI ($P = .008$) and 30% reduction in stroke ($P = .028$) than the latter. Risks of adverse CV events were similar for untreated men and treated men without T normalization. This same group found that normalization of testosterone levels is associated with a decreased incidence of atrial fibrillation, a condition often associated with increased risk of stroke.[44]

Cheetham et al[50] compared CV outcomes in men aged 40 year and older (mean age 59) with documented low testosterone values in the Kaiser Permanente system. There were 8808 men (19.8%) who received T therapy and 35 527 men (80.2%) did not. With a median follow-up of 3.4 years, the hazard ratio for adverse CV events (MI, coronary revascularization, unstable angina, stroke, transient ischaemic attack or sudden cardiac death) was lower by one-third in the T-treated group (HR 0.67, 95% CI 0.62-0.73).

Anderson et al[51] investigated MACE (death, MI, and stroke) in men with low initial T concentrations who received T therapy who either had persistently low T concentrations (<212 ng/dL, N = 801), normalized concentrations (212-742 ng/dL, N = 2241) or high concentrations (>742 ng/dL, N = 1694). Over 3 years MACE rates were reduced for men with normalized T levels compared to men with low T concentrations (HR 0.74, 95% CI 0.56-0.98) and reduced death (HR 0.65, 95% CI 0.47-0.90). MACE rates were similar for men with higher T levels compared with normal T levels.

4.3 | Meta-analyses

Two meta-analyses regarding CV risk with testosterone compared with placebo have been published since the September 2014 FDA Advisory committee meeting. One study reviewed 24 RCTs,[14] and the other reviewed 30 RCTs.[54] Neither showed increased CV risk with T treatment compared with placebo.

5 | SUMMARY OF CARDIOVASCULAR STUDIES

Although the newly added CV warning to testosterone products mandated by the FDA is technically accurate, in that some studies have reported increased CV risks and others have not, it is incomplete to note the few observational studies reporting an increased CV risk that are weak with regard to scientific evidence and quality and omit studies that provide evidence to the contrary. Specifically, the overall safety results from the Testosterone Trials revealed fewer MACE for men who received T compared with placebo by 9 to 16, respectively. A 3-year placebo-controlled trial showed no difference in progression of carotid atherosclerosis.[39] Two observational studies showed reduced hazard ratio of MACE for men whose T levels normalized with treatment compared with those whose T levels failed to normalize, indicating suboptimal treatment may increase CV risk.[44,51] Further, one study showed that longer duration of treatment was associated with reduced CV events.[42] The attention raised by the FDA investigation into CV risk appears to have prompted additional studies, together with published results from the Testosterone Trials, yet a single study has not emerged to provide evidence to support concerns that T therapy increases CV risk. On the contrary, the findings and narrative of these studies strongly suggest either a neutral or a protective CV effect for T therapy.

6 | CLINICAL INDICATIONS FOR CURRENT T PRESCRIBING: A RESTRICTED FDA LABEL CHANGE

While there may be good reason for a regulatory agency such as the FDA to restrict an indicated population, it is unusual to create a situation where the treatment for a majority of US men with T deficiency is rendered off-label so swiftly.

As noted by the International Expert Consensus Conference on Testosterone Deficiency and its Treatment,[55] there is no scientific justification to limit TTh only to men with a limited set of aetiologies, and to men younger than 65 years. Like other hormonal conditions, the symptoms and signs of T deficiency occur as a result of a deficiency of T, regardless of its aetiology. Indeed, the manifestations of T deficiency can be produced in healthy volunteers experimentally by lowering serum T. Those symptoms and signs resolve when T levels are restored to normal physiological levels. We are aware of no studies reporting greater safety of TTh in men with classical hypogonadism than any other population.

The key step to restricting the population of TTh was to remove idiopathic hypogonadism from the accepted conditions. Unfortunately, even as science progresses to identify ever-greater causes of T deficiency, the truth is that many men with symptomatic T deficiency lack a clear aetiology. Imagine restricting antihypertensive medications only to individuals with an identified cause, such as renal artery stenosis or pheochromocytoma. This would leave

approximately 80% of hypertensives untreated, despite being at risk of the morbidity associated with elevated blood pressure.

Finally, the argument that efficacy and safety have not been adequately demonstrated in men over 65 years, or in men without the set of identified, rare causes of T deficiency, is now even harder to justify. The Testosterone Trials, the largest controlled prospective trial to date, were performed exclusively in men aged 65 years and older, and in men whose T deficiency appeared related only to age. In this study, several benefits were documented, and major risks were no greater than for those who received placebo.[29-34]

7 | TESTOSTERONE TODAY

As reviewed, the weight of evidence does not support the contention that TTh increases CV risk. Indeed, for approximately two decades there was suggestive evidence that a normal endogenous serum T, or TTh itself, provided protective benefits against adverse CV outcomes. This view was challenged by two observational studies published in quick succession in late 2013 and early 2014 that reported increased CV risks and gained enormous media attention. However, a spate of new studies—controlled as well as observational—over the last 3 years has failed to support concerns of increased CV risk and has provided additional evidence that T therapy may offer CV protection in men with T deficiency. A large placebo-controlled cardiovascular T trial will be underway in the United States, and this will provide additional information regarding CV safety with TTh when it is completed in several years. Until then, we agree with the results of the International Expert Consensus Conference on Testosterone Deficiency and its Treatment and the American Association of Clinical Endocrinologists, which concluded the evidence does not indicate increased CV risk with TTh.[55]

Publicity regarding the potential for increased CV risk has also led to litigation against pharmaceutical companies that sell testosterone products, and thus, a series of bellwether suits are now underway. In our clinical practices, we have noted that this has intensified fear of litigation among providers of TTh, reduced the willingness to write a prescription and halted educational initiatives around testosterone therapy. It has fractured the clinical prescribing community into groups of those who believe TTh is of value to patients and those who believe it is dangerous, and in so doing has created a clinical quandary for the primary care clinicians who simply wish to do the best for their male patients.

Finally, the regulatory changes taken by the FDA have created a different type of challenge for clinicians by precipitously rendering TTh off-label for a majority of men with symptomatic T deficiency. While we acknowledge the critical role of regulatory agencies in protecting public health, it must also be recognized that the FDA does not regulate the practice of medicine. Numerous medical societies have published guidelines or recommendations regarding TTh, none of which follow FDA restrictions on age or aetiology. As with many scientifically supported off-label uses of medications or treatments which form routine medical practice, clinicians must apply their own judgement based on available evidence to determine whether their patients may benefit from a given treatment, including TTh.

CONFLICT OF INTEREST

Dr. Martin Miner declares no conflict of interest. Dr. Abraham Morgentaler is consultant to AbbVie, Acerus, Antares, Bayer, Besins, Endo, Pfizer and Repros. Dr. Mohit Khera is consultant to AbbVie, Endo, Boston Scientific and Coloplast. Dr. Abdulmaged Traish is a consultant to Repros.

AUTHOR CONTRIBUTIONS

All authors performed conception and/or design, data interpretation and writing.

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