INVITED COMMENTARY

Perspective: Regulatory Agencies' Changes to Testosterone Product Labeling

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A biochemical decrease in circulating testosterone (total testosterone, TT ≤ 10.4 nMol/L or 300 ng/dL) is a relatively common condition, particularly in aging men. Data derived from a Florentine sub-analysis of the European Male Aging Study indicate that, in this geographic area, 8% of the general population, aged 40 years or older, have the condition, although asymptomatic [1]. However, all the guideline recommendations of dedicated scientific societies suggest that the diagnosis of late-onset hypogonadism (LOH) must be considered only in the presence of specific symptoms. It is well recognized that sexual dysfunctions are the most specific symptoms characterizing male hypogonadism (HG) during adulthood [2].

In a large series of subjects consulting an andrology unit for sexual dysfunction in Florence, overt HG was present in 20% of the entire cohort [1]. Hence, having sexual dysfunction appears to double the chance of having low testosterone (T). Currently, the question is whether it is safe for the sexual medicine clinician to prescribe T preparations for subjects with low T and specific symptoms. The answer is not easy, in particular considering recent claims on safety and on the reported increased risk of cardiovascular (CV) events associated with T use [3]. The Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh), a regulatory body representing European Member States—after a review by the European Medicines Association (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC)—has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with T medicines in HG men (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Testosterone-containing_medicines/human_referral_prac_000037.jsp&mid=WC0b01ac05805c516f). PRAC also noted that the lack of T itself could increase the risk of heart problems. However, the use of T in healthy older men is not an authorized use in the European Union (EU, http://www.ema.europa.eu). A few months after the EMA's PRAC position statement, the cognate U.S. agency, the Food and Drug Administration (FDA), released an opposite opinion for a possible elevated CV risk associated with starting or continuing T therapy (http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm). The FDA cautions that prescribing T products is approved only for men who have low T levels caused by certain medical conditions. In particular, only subjects with primary or secondary HG (sHG) resulting from problems within the testis, pituitary, or hypothalamus (e.g. genetic problems, or damage from surgery, chemotherapy, or infection) should be treated. In contrast, the FDA emphasized that the benefits and safety of T medications have not been established for the treatment of low T levels due to aging, even if a man's symptoms seem related to low T. In other words, only hypogonadal men with a well-defined etiological condition must be systematically treated, but not those with an age-related T decrease. Table 1 shows the main causes of HG (i.e. ≤10.4 nMol/L or 300 ng/dL) in a large series of men consulting for sexual dysfunction in Florence (n = 4220), categorized according to LH levels [4]. Only in one half of the cases of primary HG can an etiological condition be identified. Klinefelter syndrome accounts for the majority of testicular disor-

Table 1 Causes of primary and secondary hypogonadism in a large series of subjects (n = 4220 mean age) seeking medical care for sexual dysfunction between 2000 and 2014 at our Unit [4]

Underlying cause	Primary (%)	Secondary (%)
Overall	3.2	17.4
Unknown	50.4	89.0
Infections	6.0	—
Testis surgery or chemotherapy	8.4	—
Radiotherapy	2.6	1.1
Cryptorchidism	5.1	—
Congenital anorchia	0.9	—
Genetic		
Klinefelter	23.1	—
Myotonic dystrophy	0.9	—
Kallmann syndrome	—	1.1
End-stage renal diseases	1.7	0.1
Drug induced	0.9	2.4
Empty sella	—	1.7
Pituitary surgery	—	3.4
Head trauma	—	0.1
Prolactin secreting adenoma	—	1.1

Gonadal status was identified according to the European Male Aging Study criteria [5]: normal or eugonadal (T ≥ 10.5 nmol/L and LH ≤ 9.4 U/L), secondary hypogonadism (T < 10.5 nmol/L and LH ≤ 9.4 U/L), primary hypogonadism (T < 10.5 nmol/L and LH > 9.4 U/L)

ders. The figure is even more impressive when sHG is considered. In this case, a causal condition can be inferred only in 10% of the subjects. This is particularly interesting, because, as stated before, sHG is by far the most prevalent form of LOH. Therefore, according to FDA criteria, more than 85% of the symptomatic subjects with low T consulting for sexual dysfunction should not be treated, because the T decline is "age-related" and therefore treatment would put patients at risk for cardiac or other major adverse CV events (MACE). Is this indication evidence based? We recently published a meta-analysis restricted to T placebo-controlled randomized controlled trials (RCTs) on different primary outcomes because studies with T and specific CV endpoints as the primary outcome were few and of short duration [6]. Our systematic review did not substantiate the view that T treatment brings with it any additional risk of CV-related adverse events, when HG is properly diagnosed and replacement therapy correctly performed. When a separate analysis was performed according to the baseline population characteristics, similar results were obtained even in studies enrolling subjects with an age-related condition [6]. Recently, results from the TSAT study have been reported [7]. This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 16-week trial on T supplementation in 596 adult, hypogonadal men with decreased energy or decreased sexual drive [7]. By combining the results from this study with those from the aforementioned meta-analysis on RCTs performed after excluding those trials enrolling subjects with a well-known cause of HG [6], we now show (Figure 1) that the use of T is not associated with any significant difference in the incidence of MACE (MH-OR: 0.89 [0.50–1.61]; $P = 0.70$) suggesting, in aging men, a neutral effect of T substitution on MACE outcomes. Similar results were obtained when any CV-related events were considered (not shown).

We are not convinced at all that T really declines as a factor of age. According to the EMAS study [5], in sHG, the age-associated chronic morbidities, rather than age per se, better explain the decline of gonadotropins and T observed in aged men. The most frequent chronic conditions associated with sHG are obesity, metabolic syndrome (MetS), and diabetes [4]. Accordingly, in our population almost three-fourth of cases of the unknown causes of HG can be attributed to the aforementioned conditions (71.8% for primary HG and 70.7% for sHG). We recently reported in a rabbit model of MetS, characterized by sHG, the presence of hypothalamus inflammation and a decrease of several genes involved in the formation and release of GnRH [8]. In translational medicine, this indicates that metabolic disturbances are associated with discrete abnormalities in the arcuate nucleus of the hypothalamus, such as the other "organic" problems mentioned by the FDA. Whether or not treating MetS will attenuate GnRH-related hypothalamic alterations is under evaluation in this animal model. However, a recent meta-analysis of RCT studies indicates that, in humans, decreasing weight is associated with a sustained increase in both gonadotropin and T levels [9]. Hence, the first therapeutic approach in a subject with age-related HG should be changing lifestyle behavior and treating overweight/obesity or other underlying conditions. However, if this strategy fails—or even as a support for this strategy—T treatment must be considered. In fact, T substitution is able to decrease abdominal fat accumulation and increase muscle mass and insulin sensitivity, therefore facilitating weight loss [3]. In a small series of RCT on T substitution in men with metabolic diseases, it was even demonstrated, by meta-analysis, that T administration decreases (not increases) MACE [6].

In conclusion, we strongly believe that the categorical distinction between "organic" and "age-related" HG is unrealistic, at least as far as sHG is concerned. In age-related, metabolic condition-