ABSTRACT

Introduction: The role of testosterone (T) replacement therapy (TRT) in men is still conflicting. In particular, safety concerns and cardiovascular (CV) risk related to TRT have not been completely clarified yet. Similarly, the clear beneficial effects of TRT are far to be established.

Aim: To systematically and critically analyze the available literature providing evidence of the benefit-risk ratio derived from TRT in aging men.

Methods: A comprehensive PubMed literature search was performed to collect all trials, either randomized controlled trials (RCTs) or observational studies, evaluating the effects of TRT on different outcomes.

Main Outcome Measure: Whenever possible, data derived from RCTs were compared with those resulting from observational studies. In addition, a discussion of the available meta-analyses has been also provided.

Results: Data derived from RCT and observational studies clearly documented that TRT can improve erectile function and libido as well as other sexual activities in men with hypogonadism (total T < 12 nM). Conversely, the effect of TRT on other outcomes, including metabolic, mood, cognition, mobility, and bone, is more conflicting. When hypogonadism is correctly diagnosed and managed, no CV venous thromboembolism or prostate risk is observed.

Clinical Implications: Before prescribing TRT, hypogonadism (total T < 12 nM) must be confirmed through an adequate biochemical evaluation. Potential contraindications should be ruled out, and an adequate follow-up after the prescription is mandatory.

Strength & Limitations: When correctly diagnosed and administered, TRT is safe, and it can improve several aspects of sexual function. However, its role in complicated vasculogenic erectile dysfunction is limited. Conversely, TRT is not recommended for weight reduction and metabolic improvement. Further well-powered studies are advisable to better clarify TRT for long-term CV risk and prostate safety in complicated patients as well as in those curatively treated for prostate cancer.

Conclusion: TRT results in sexual function improvement when men with hypogonadism (total T < 12 nM) are considered. Positive data in other outcomes need to be confirmed.

Key Words: Testosterone; Testosterone Replacement Therapy; Sexual Desire; Erectile Dysfunction; Cardiovascular Risk; Prostate Cancer
borderline low T levels, mainly associated with sexual symptoms, where the risk/benefit ratio of TRT is more debated. Lifestyle changes and/or removing the underlying condition is the recommended strategy to increase endogenous T levels. This position has been recently endorsed by the U.S. Endocrine Society and, even before, by the Endocrine Society of Australia. Accordingly, the U.S. Food and Drug Administration (FDA) along with Health Canada recommends TRT only in those subjects with proven “organic” damage of the hypothalamic-pituitary-testis axis.

To shed light on the possible benefits of TRT in the aging male, in 2003, the U.S. National Institute on Aging funded a set of clinical trials. Testosterone Trials (TTrials) were then designed and performed as a coordinated set of 7, 52-week randomized placebo-controlled, double-blind trials (RCTs), including 788 men with hypogonadism (TT < 9.4 nM) older than 65 years (mean age 72 years) treated with T gel 1%, in the active arm. The results of these studies have been published throughout the last 2 years, providing new evidence on the effects of TRT on aging men.

The aim of this review is to systematically and critically analyze the available literature on the effects of TRT on different outcomes in aging men. In addition, to better clarify the different positions released by medical agencies around the world on this topic, a revision of a worldwide pattern of TRT prescriptions, observed in the last years, is also reported.

METHODS

The analyses have been conducted based on extensive Medline search for the identification of all trials, either RCTs or observational studies, evaluating the effects of TRT on aging men. The search was conducted including the following keywords ("testosterone"[MeSH Terms] OR "testosterone"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("humans"[MeSH Terms] AND English [lang] AND “male”[MeSH Terms]). Publications from January 1, 1969, up to June 1, 2019, were included. When possible, data derived from RCTs were compared with those arising from observational studies. In each section, the results deriving from the TTrials were closely analyzed and discussed. In addition, results from the available meta-analyses were also provided. Meta-analyses have been suggested for addressing questions for which multiple data sources are in conflict or fail to reach a consensus. In addition, meta-analysis evaluation is particularly useful when there are a variety of reports with low statistical power, as pooling data can improve power and provide a convincing result. Finally, a specific section was dedicated to the safety concerns related to TRT.

PATTERN OF T PRESCRIPTION

T was chemically synthesized for the first time in 1935 simultaneously by Butenandt group in Gottingen and by Ruzicka and Wettstein in Basel. After its synthesis, T preparations soon became available for clinical use, first in the form of pellets and then as injectable esters. Although T products have been available for almost 80 years, the introduction on the market of more manageable preparations, including gels and long-acting injectable formulations, has dramatically expanded the T business over the last 2 decades. This phenomenon is particularly evident in the United States and Canada, where the possibility to release specific drug- and disease-related advertisements has clearly influenced the market.

Conversely, during the same period, European T sales remained more stable. Besides the aforementioned pattern, at least 3 large reports, analyzing commercial insurance data, have emphasized a clear misuse of T prescriptions. In a U.S. claim database survey, Baillargeon et al. found that among a total of 10,739,815 men, aged 40 years or older, who were prescribed TRT, between 2001 and 2011, only 74.7% had their T measured prior to the prescription. Similar data have been reported by Muram et al. through the analysis of another U.S. Insurance Database. Finally, an evaluation of all outpatient clinics within Veterans Affairs (VA), during fiscal years 2009–2012, of patients who had not previously received TRT and received at least 1 T dispensing during the study period, showed that only 3.1% of them underwent an ideal biochemical and clinical evaluation before starting therapy. Similarly, the same studies have documented that TRT was often prescribed only based on unspecific symptoms including fatigue, weakness and depressed mood, symptoms often present in aging men.

TRT OUTCOMES

The previous section has clearly illustrated that some form of T overuse or misuse has been present since 2000 in everyday clinical practice. Whether or not this pattern has influenced claims regarding TRT safety in aging men is still a matter of intense debate. However, it is important to recognize that all available guidelines recommend treating with T only symptomatic men who present documented reduced T levels, after appropriate testing. In this section, available evidence of TRT on different outcomes will be provided and analyzed.

Sexual Function

T profoundly regulates all aspects of sexual function and, in particular, erectile function and libido. In fact, all available meta-analyses have clearly shown that TRT is effective in restoring sexual desire and libido in men with hypogonadal total T < 12 nM; 18 and Table 1). Conversely, no effect was documented when TRT was administered to subjects with normal total T, that is above 12 nM. Overall, TRT resulted in a mild to moderate effect in the vast majority of the available meta-analyses (Table 1). Sexual effects were proportional to the increase in T concentration and higher on libido, when compared with erectile dysfunction (ED). A meta-analysis including only RCTs based on the International Index of Erectile Function scoring as the final outcome documented that TRT is able to improve erectile function domain by 2.3 points. According to Rosen et al., this increase could be considered
clinically meaningful only in subjects with mild ED and not in those with more severe forms. Furthermore, it has been reported that a higher prevalence of organic conditions, such as obesity and diabetes, underlining possible vascular damage, attenuated the positive effect of TRT on patients with ED.18,19

The aforementioned data are in line with what was derived from the TTrials (Table 1).10 Final results showed that TRT, as compared with placebo, increased sexual interest and sexual activity, from flirting to sexual intercourse, with a moderate effect size, which was inversely related to the baseline T levels and proportional to the increase in T levels during the study.10 A greater effect on libido and sexual activity than on erectile function was observed.10

Similar data can be derived from observational, open-label surveys, which often report even better outcomes for TRT in improving all aspects of sexual function (Table 1).18,19

The data observed for libido and ED are not surprising. In fact, besides hormones, several other factors including psychiatric, relational, or pharmacologic conditions can influence sexual desire,17 explaining, at least partially, the limited effects of TRT on libido. In addition, it is important to recognize that the close association between cardiovascular (CV) risk factors and ED can justify the limited role of TRT alone in improving erectile function in more severe forms of ED. The combination of TRT and phosphodiesterase type 5 inhibitor (PDE5i) has been suggested in the latter cases. Only one meta-analysis published so far has investigated this issue.22 The data confirmed the possible advantages of using the combined therapy when placebo- and nonplacebo-controlled trials were considered. However, when the analysis was restricted to only placebo-controlled RCTs, the significance of the effect was lost. It is important to recognize that only a limited number of trials were available at that time and that many of them enrolled a mixed population of subjects with eugonadism/hypogonadism.22

The possible role of TRT in improving ejaculatory function represents another conflicting issue (Table 1). An association between delayed ejaculation and reduced T concentrations has been reported, although not confirmed in all studies.18,19 Several register observational surveys have documented that axillary T gel 2% improved all the aforementioned areas, when compared with placebo.23 This was confirmed in the meta-analyses specifically evaluating this issue, although only a limited number of studies were available.20,22 Hence, although some

| Table 1. Summary of testosterone replacement therapy (TRT) outcomes |
|------------------|------------------|------------------|------------------|------------------|
| TRT outcomes     | TTtrials         | Other RCTs       | Observational studies | Meta-analyses |
| Sexual function  | T T T T           | T T T T         | T T T T T T T T T | T T T T T T T |
| Erectile dysfunction | ↑ ↑ ↑ ↑       | ↑ ↑ ↑ ↑         | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↑ ↑ ↑ ↑ |
| Libido           | ↑ ↑ ↑ ↑       | ↑ ↑ ↑ ↑         | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↑ ↑ ↑ ↑ |
| Ejaculation      | NA            | ↑ ↑ ↑ ↑         | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↑ |
| TRT + PDE5i      | NA            | ↑ ↑ ↑ ↑         | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↔ |
| Erectile dysfunction | NA            | ↑ ↑ ↔          | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↔ |
| Body composition |               | T T T T T T T T | T T T T T T T T | T T T T |
| Fat mass         | NA            | ↓ ↓ ↓          | ↓ ↓ ↑ ↑ ↑ ↑ ↑ ↑ | ↓ |
| Lean mass        | NA            | ↑ ↑ ↑          | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↑ |
| Body mass index  | NA            | ↓ ↓ ↓          | ↓ ↓ ↑ ↑ ↑ ↑ ↑ ↑ | ↓ |
| Weight           | ↔             | ↑ ↑ ↑          | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↔ |
| Metabolic control|               | T T T T T T T T | T T T T T T T T | T T T T |
| Glucose metabolism | NA             | ↑ ↑ ↔         | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↑ |
| Lipid profile    | NA            | ↑ ↑ ↔          | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↑ ↔ |
| Blood pressure   | NA            | ↔             | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↔ |
| Bone             |              | T T T T T T T T | T T T T T T T T | T T T T |
| Bone mass        | ↑ ↑ ↑          | ↑ ↑ ↑          | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↑ |
| Fracture risk    | NA            | NA            | NA              | NA |
| Mood/cognition   |               | T T T T T T T T | T T T T T T T T | T T T T |
| Depressive symptoms | ↑ ↑ ↑        | ↑ ↑ ↑          | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↑ |
| Cognition        | ↔             | ↔             | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | NA |
| Mobility         | ↑ ↑ ↔          | ↑ ↑ ↔          | ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ | ↑ |

Arbitrary unit (↑) is indicated as follows: ↑ = mild, ↑ = moderate, ↑ = strong effect. ↑, ↓, and ↔ indicate positive effect, negative effect, and neutral effect, respectively.

NA = not available; PDE5i = phosphodiesterase type 5 inhibitor; RCTs = randomized controlled trials; TRT = testosterone replacement therapy; TTrials = testosterone trials.
positive evidence suggests that TRT can improve ejaculation and orgasmic function, more placebo-controlled RCTs are advisable to confirm this effect.

**Obesity**

A large body of evidence has shown that overweight and obesity represent risk factors for the development of secondary HG,24,25 Accordingly, longitudinal data from the European Male Aging Study have shown that obesity at the baseline and weight gain during follow-up increased the risk, whereas subjects who lost weight during the study were more prone to recover from secondary HG.26,27 The specific mechanisms underlying obesity-associated HG have not been completely clarified. However, a working hypothesis is that the metabolic derangements associated with obesity can act either at a central or at a peripheral level, inducing the development of mixed or, more frequently, secondary HG.24,28 Only few RCTs have specifically evaluated the effect of TRT on obese individuals (Table 1). Fui et al32 showed that in obese men (body mass index [BMI] \( \geq 30 \) kg/m\(^2\)) with a repeated total T concentration < 12 nM, receiving a very low-energy diet, TRT is able to improve body composition (reduction of fat mass and increase of lean mass), without any difference in final weight, when compared with placebo. Similar results were derived from a recent meta-analysis investigating the effect of TRT in available placebo-controlled RCTs (Table 1).30 Interestingly, the latter meta-analysis documented that TRT caused equal modifications in fat and lean mass, which can explain the lack of change observed in final weight and in the BMI.30 The main limitation of the available RCTs is the short duration of the follow-up (< 3 years). Hence, possible long-term effects of TRT on body composition are unknown. Data derived from observational and uncontrolled studies, with a longer follow-up, suggest that TRT can eventually induce a reduction of body weight and BMI, after at least 2 years of treatment (Table 1).31 However, it is important to recognize that uncontrolled studies present important limitations because residual confounding factors may represent a source of selection bias in accordance with the nonrandom assignment of T exposure. In fact, physicians often prefer to treat healthier individuals, and healthier individuals more often request treatment for their HG-related problems, thus accounting for better outcomes in this group.

Meta-analyses of available evidence clearly documented that weight loss, however obtained (low calorie diet or bariatric surgery), and/or physical activity are able to improve T concentrations and to revert obesity-associated HG.35 Hence, lifestyle modifications should be the first approach for improving body composition and for increasing T levels in obese individuals. However, the magnitude of T increase after lifestyle modifications is rather modest (about 2 nmoles/L; 32). Furthermore, therapeutic diets and behavioral modifications—although reasonable strategies for protecting against obesity-associated HG—often fail, and a large proportion of subjects regain weight during follow-up. In addition, an open question is whether obese, individuals with hypogonadism individuals have the skills to progress safely and effectively along the continuum of changing their lifestyle. For instance, physical limitations, including reduced muscle mass and increased fat mass, might limit their propensity to increase physical activity. It is therefore conceivable that a short-term TRT trial, by improving muscle mass, will help obese patients with HG to overcome their overfed, inactive state to become physically and psychologically ready for changing their lifestyle. On the other hand, a combined approach with a controlled dieting program and TRT might result in a better outcome. Accordingly, by combining the available evidence with a meta-analytic approach, we previously reported that TRT might result in better outcomes when compared with lifestyle modification alone.33 However, it should be recognized that the number of the available trials, and the related amount of patients enrolled, is too limited to draw conclusions.

**Metabolic Syndrome and/or Type 2 Diabetes**

The role of TRT in improving metabolic derangements occurring in type 2 diabetes (T2DM) and metabolic syndrome (MetS) is conflicting. Only limited numbers of placebo-controlled RCTs have specifically investigated the effect of TRT in these populations (Table 1). TIMES-2, the largest study performed in either T2DM or MetS subjects (n = 220) was not able to document a significant reduction in HbA1 concentrations or the BMI after 26 weeks of T gel 1%, although an improvement in Homeostatic Model Assessment of Insulin Resistance was reported.34 This was confirmed even when only patients with T2DM were analyzed.34 The largest RCT conducted only on T2DM is the BLAST (an acronym taken from the UK cities and towns of Birmingham, Lichfield, Atherstone, Sutton Coldfield, and Tamworth) study, which included 199 men recruited from 7 UK diabetes registers.35 After 30 weeks, long-acting injectable testosterone undecanoate (TU) resulted in a significant improvement of HbA1 concentrations, particularly in poorly controlled men (baseline HbA1c \( \geq 58 \) mmol/mol; 7.5%) and a decrease in waist circumference, without any significant modification in the BMI.35 In contrast to these observations, Gianatti et al166 did not observe any improvement in HbA1 concentrations or the Homeostatic Model Assessment of Insulin Resistance index in 88 men with T2DM after 40 weeks of long-acting injectable TU, when compared with placebo. However, as reported in the general population,30 an improvement in body composition (reduction of fat mass and increase in lean mass) was documented in the active arm.36 Similar considerations can be derived from available meta-analyses, which documented a limited improvement of fasting glycemia and insulin resistance, with even poorer results when only high-quality trials were considered (Table 1).37

Long-term registry studies have shown that TRT might improve glycometabolic control in men with T2DM and MetS, up to 8 years (Table 1).38–41 The results of these studies present important limitations, as reported previously. However, it should be recognized that the longer follow-up and the differences in the
characteristics of the subjects treated in the observational studies could explain, at least partially, the difference observed when compared with placebo-controlled RTCs. Despite these considerations, present evidence suggests that possible contributions of TRT on glycometabolic outcomes are limited, and TRT cannot be suggested as an alternative treatment for T2DM or MetS.

The effects of TRT on other parameters of MetS such as lipid profile and blood pressure are even more conflicting, and the available evidence is too limited to draw any conclusions (Table 1).

Bone

Much evidence has documented that bone health requires circulating sex steroids within the normal range. T concentrations can differentially interfere with bone homeostasis and the risk of osteoporosis. The possible association between mild HG and osteopenia/osteoporosis is weak, whereas severe HG (total T < 3.5 nM) is frequently associated with bone loss and osteoporosis, independently from the patient’s age. 2 independent meta-analyses showed a positive effect of TRT on bone mineral density (BMD), with a higher effect at the lumber level. Insufficient data have been published to calculate the effect of TRT on the risk of bone fractures. In addition, the contribution of TRT on top of antiresorptive treatments in patients with hypogonadism patients at a high risk of fractures has not been established. Hence, antiresorptive therapy must be the first choice of treatment in men with hypogonadism at high risk for bone fracture. The combination with TRT should be offered in the presence of HG-related symptoms.

Mood

Several observational studies have documented a relationship between depressive symptoms and reduced T concentrations. The specific relationship between HG and the incidence of clinical depression are still unclear. Data derived from the TTrials showed that TRT modestly improved mood and depressive symptoms, using several instruments. In line with these data, the largest meta-analysis published so far, including 1890 men with HG (baseline total T < 12 nmol/L or fT < 225 pmol/L) from 27 RCTs, documented that a positive effect of TRT on depression was particularly evident only in patients with milder symptoms. Information regarding the combination between an established depressive therapy and TRT is unknown.

Cognition

Reduced T levels have been associated with a precarious cognitive impairment in subjects treated with androgen deprivation therapy for prostate cancer (PC) and in individuals from the general population. Despite this evidence, however, the role of TRT in patients with cognitive impairment is still conflicting. Among the TTrials, the Cognitive Function Trial was aimed at assessing the possible improvement of several aspects of cognitive function in 493 individuals with age-associated memory impairment. The trial failed to demonstrate any effect of TRT on improving cognitive function, as assessed by a wide range of tests.

Mobility

T has been able to increase muscle growth and strength in several experimental models. Taking advantage of this anabolic effect, androgenic steroids have been used for increasing physical performance in an abusive way in several sport competitions. Despite this evidence, the role of TRT in older men with mobility limitations remains unclear. Steeves et al were unable to detect any association between overall circulating T levels and the amount of physical activity using data from men enrolled in the National Health and Nutrition Examination Survey, a series of studies designed to assess the health and nutritional status of adults and children in the United States. Similarly, the Physical Function and Vitality Trials from the TTrials indicated that TRT did not substantially result in any improvement on several physical vitality tests, including the fraction of men whose distance walked in 6 minutes increased more than 50 m or the absolute increase in the distance walked. However, when the whole population of the TTrials was considered, a significant, although modest, positive effect on these 2 parameters was reported. Similarly, a previous meta-analysis of the available data documented only dominant knee extension and dominant handgrip, which showed a tendency toward improvement with T over placebo. Hence, TRT should not be used to improve mobility in aging men.

Role of TRT in Specific Subpopulations

Several chronic unhealthy conditions have been associated with reduced T levels. A limited number of RCTs have assessed a possible role of TRT in populations with these conditions. This aspect represents the main limitation for a critical evaluation. In addition, the population included in the few available RCTs is often made up of a combination of men with hypogonadism and men with eugonadism representing another crucial limitation in data analysis. Hence, available evidence does not suggest using TRT to improve mortality or morbidity in these populations (refer the following section).

Subjects with HIV Infections

HIV-1 infection, and in particular wasting syndrome, is frequently associated with a reduced T concentration. In addition, men infected with HIV often show a premature decline of serum T associated with inappropriately low/normal luteinizing hormone level and with increased visceral fat. Fortunately, the era of antiretroviral therapy has dramatically reduced the occurrence of wasting syndrome. Nonetheless, chronic involuntary weight loss remains a serious problem in subjects with HIV. Johns et al published the first meta-analysis of the available 4 RCT studies comparing the use of anabolic steroids vs placebo for treating weight loss in adult men and women infected with HIV. They
showed that anabolic steroids resulted in a small increase in both lean body mass and body weight. We reported an updated meta-analysis on the same topic, confirming the positive result on lean mass.53 These data were confirmed in a more recent meta-analysis on the same topic, which included 14 eligible studies.54

The main limitations related to the published meta-analyses on this topic are the limited number of available placebo-controlled RCTs and the high heterogeneity among the different studies.

Opioid-Treated Subjects

The association between reduced T concentrations, androgen deficiency, and opioid treatment has been documented since the 1970s, when reports emerged in men who were on maintenance methadone therapy.55 Available studies evaluating the impact of opioid treatment on T concentrations in men with chronic non-cancer pain show that the prevalence of opioid-induced androgen deficiency ranges from 19% to 86%, depending on the considered T threshold.53 Discontinuing opioids may be an option for symptomatic men with reduced T concentrations. If pain relief with nonopioids is inadequate, or patients are unable to discontinue opioid treatment, TRT should be considered. A limited number of studies have evaluated the effects of TRT on men with opioid-induced androgen deficiency. In the only placebo-controlled RCT available, TRT reduced mechanical hyperalgesia and improved sexual desire and overall quality of life.56 The improvement of sexual function and pain relief after TRT has been confirmed in other prospective and retrospective observational trials.55

Long-Term Glucocorticoid Therapy—Treated Subjects

Long-term glucocorticoid (GC) therapy is the most common cause of iatrogenic osteoporosis, accounting for 30%—50% of bone fractures. GC treatment is frequently associated with male HG by inhibiting the secretion of gonadotropins and by inhibiting Leydig cell function.57 Adult men on GC who develop HG should theoretically benefit from TRT. However, limited information is available. In the first placebo-controlled RCT, involving 51 men on a mean daily prednisone dose of 12.6 ± 2.2 mg, TRT increased muscle mass, muscle strength, and lumbar spine BMD after 12 months.57 Similar results were previously reported in a non—placebo-controlled RCT dealing with GC-treated asthmatic men.58

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) represents another chronic condition frequently associated with male HG.53 An available meta-analysis, including only 9 observational studies and 2,918 men with COPD, concluded that TRT did not improve exercise capacity outcomes, including peak muscle strength and peak workload.59 Limited evidence for improving lean mass in men with COPD and hypogonadism treated with TRT has been reported.53 However, the vast majority of the interventional trials evaluating the effect of TRT in this population are nonplacebo-controlled trials, further limiting the evidence.

Chronic Kidney Diseases

Impaired renal function in chronic kidney diseases, and, in particular, in end-stage renal diseases is frequently associated with male HG.53 Some prospective studies have documented that a low level of T can be considered an independent risk factor for the progression of the disease and for overall mortality in this population.60 However, placebo-controlled RCTs specifically evaluating the effect of TRT in subjects with chronic kidney disease or end-stage renal disease are lacking.

Inflammatory Bowel Diseases

Data derived from an animal model and clinical observational studies have suggested a possible anti-inflammatory effect of TRT.61,62 Some registered studies have documented that normalization of T concentrations in men with hypogonadism with Crohn’s disease might have a positive effect on the clinical course of the diseases, also evidenced by the improvement of some biochemical parameters.63,64 No RCTs specifically evaluating the effect of TRT in patients with inflammatory bowel diseases are available so far. In addition, data derived from observational studies have not been replicated by other groups.53

SAFETY

Safety concerns remain one of the most conflicting issues related to TRT in age-related or functional HG. In particular, CV safety, as well as prostate safety, still represents hot and not completely clarified topics. The evidence related to these subjects will be analyzed in detail in the section “Cardiovascular Safety.”

Cardiovascular Safety

Few studies (one RCT, 2 observational surveys, and one meta-analysis) published between 2010 and 2014 created a great claim in the scientific community, emphasizing a possible increased CV risk related to TRT.65–68 These studies present important limitations already recognized elsewhere.69–71 However, taking into consideration the results of these studies, in 2015, the FDA issued a safety notification regarding the misuse of T-containing products, due to a potential CV and thromboembolic risk. Soon after, similar considerations were released by Health Canada.9 Conversely, the European Medical Agency did not share the FDA’s opinion of an increased CV risk linked to T medication because of the lack of convincing evidence.65 These contradictory positions deserve further consideration.

Overall CV Risk

The first study suggesting a possible increased CV risk related to TRT was the “Testosterone in Older Men with Mobility Limitations” (TOM) trial, a double-blind placebo-controlled RCT aimed at evaluating possible improvements in several mobility outcomes among more than 200 men with hypogonadism with mobility limitations.65 The study was prematurely interrupted because of higher CV-related events in the
active arm. However, several limitations have been recognized. The population enrolled was based on a large group of men with a high prevalence of associated morbidities that were treated with a supraphysiological dose of T gel (100 mg daily). In addition, CV events were not adjudicated. In addition, several minor CV problems, including self-reported syncope and peripheral edema, were considered as CV events. More recently, data related to the CV trial, within the TT trials, have become available. The study involved 138 subjects, and the primary outcome was to test the hypothesis that TRT would improve a surrogate CV outcome such as noncalcified coronary artery plaque volume, as determined by computed tomographic angiography. The result of this trial shows that TRT significantly increased coronary artery plaque progression during 12 months of treatment. Even in this case, several flaws should be recognized. A larger non-calcified plaque volume at enrollment was present in the placebo arm, when compared with that in the active group (317 vs 204 mm³). In addition, although the plaque volume showed a greater increase in the active arm, men enrolled in the T-groups still had a lower volume at the end point (232 vs 325 mm³). Moreover, at the end point, no differences between groups were observed in other important outcomes, such as coronary calcium score and the incidence of CV events among groups.

As reported previously, along with the aforementioned RCTs described, 2 pharmacoepidemiological surveys contributed to the position supporting an increased CV risk related to TRT. In the first study, published in 2013, Vigen et al retrospectively analyzed data including 8,709 American veterans (VA) who underwent coronary angiography between 2005 and 2011. The Authors reported that among men with hypogonadism (total T < 10.4 nmol/L), those who were prescribed TRT had an increased risk of major adverse cardiovascular events (MACEs) or death from any cause, when compared with those who did not use the same treatment. Soon after the publication of this study, Finkle et al reported similar data by analyzing a large Medicare insurance database including 55,593 subjects. In particular, they showed that TRT was associated with a 2-fold increased risk of heart attack among men aged 65 years and older, which was particularly evident in younger men with a preexisting history of heart disease. Both studies present important limitations. The main problem deals with the lack of information concerning T dosing and measurements during the follow-up. In addition, the comparison group included in the study by Finkle et al was composed of 167,000 subjects who were prescribed a PDE5i. The PDE5i has well-known cardio-protective effects, which should be considered in the data evaluation. Besides the latter studies, several other pharmacoepidemiological reports have investigated the possible relationship between TRT and CV risk. In a first qualitative analysis of these reports, Alexander et al concluded that all studies were characterized by a high clinical and methodological heterogeneity and by a very low quality. Interestingly, by using a meta-analytic method, we recently confirmed Alexander et al's results on a high heterogeneity within these types of studies, but we were unable to confirm a risk of publication bias. In addition, our conclusion was that, when overall mortality and CV mortality and morbidity were considered, TRT resulted as being protective and not harmful. However, it is important to recognize that only a limited number of studies were available with overall poor quality, due to the lack of crucial information such as the level of T before and during TRT, the number of the blood samples drawn during treatment, the type of T preparations used, the dropout number, and the level of hematocrit.

RCTs are usually considered the gold standard for testing the effect of a specific treatment. Until now, 9 systematic meta-analyses evaluating the effect of TRT on CV risk from placebo-controlled RCTs are available (Supplementary Table 1). The included amount of trials ranges from 19 to 75, and the number of subjects considered ranges from 1,084 to 8,479. 7 meta-analyses reported outcomes on aggregate CV events as their primary end point, whereas one investigated disaggregate events. In addition, disaggregate events were also analyzed by 6 studies, whereas 2 reported only aggregate analyses (Supplementary Table 1). Table 2 shows that only Xu et al reported an increased CV risk related to TRT. Conversely, no other meta-analyses found an increased CV risk related to TRT, when either aggregate or disaggregate CV events were considered (Table 2). Is important to recognize that, similar to what was observed in the TOM trial, the meta-analysis by Xu et al considered a broader definition of CV events, causing an artificial increase of the overall number of events. Some authors in their meta-analysis have suggested possible differences in CV risk when the different T preparations were considered. In particular, Borst et al suggested an increased CV risk related to the use of oral formulations, whereas Albert et al reported a possible increased risk using transdermal preparations, when the analysis was restricted to trials lasting less than 12 months. However, the largest and most updated meta-analysis did not confirm these data, suggesting a neutral effect when both aggregate or disaggregate events were considered, independently from the T preparation considered. Interestingly, our report showed that an increased CV risk was observed when T was prescribed at a higher dosage than those recommended by the available guidelines or when frail men were considered.

**Erythrocytosis Risk**

Increased hematocrit has been inconsistently reported to be a risk factor for cardiovascular morbidity, mortality, and venous thromboembolism (VTE). The specific threshold related to an increased CV risk is still a matter of intense discussion. In particular, although a hematocrit >54% is considered a well accepted indication for TRT withdrawal and phlebotomy, the standard level of hematocrit to be considered for starting TRT is conflicting. Much evidence has documented that TRT can increase hematocrit through different mechanisms, including direct (positive action on bone marrow erythroid progenitor...
Table 2. Odds ratio for aggregate or disaggregate cardiovascular (CV) events as derived from the available meta-analyses

<table>
<thead>
<tr>
<th>Meta-analyses considered</th>
<th>CV risk</th>
<th>Overall CV events MACE</th>
<th>AMI</th>
<th>Acute coronary syndrome</th>
<th>Coronary by-pass surgery</th>
<th>Stroke</th>
<th>Arrhythmias</th>
<th>New heart failure</th>
<th>CV mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calof et al, 200577</td>
<td></td>
<td>1.22 [0.53;2.81]</td>
<td>-</td>
<td>0.99 [0.44;2.26]</td>
<td>0.93 [0.39;2.26]</td>
<td>0.79 [0.35;1.79]</td>
<td>0.86 [0.38;1.95]</td>
<td>1.22 [0.53;2.81]</td>
<td>-</td>
</tr>
<tr>
<td>Haddad et al, 200778</td>
<td></td>
<td>1.82 [0.78;4.23]</td>
<td>-</td>
<td>2.24 [0.51;10.02]</td>
<td></td>
<td>3.703</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Fernández-Balsells et al, 201079</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.35 [0.26;6.96]</td>
<td>-</td>
<td>3.00 [0.32;27.94]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Xu et al, 201368</td>
<td></td>
<td>1.54 [1.09;2.18]</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
<td>1.42 [0.70;2.89]</td>
<td>-</td>
</tr>
<tr>
<td>Corona et al, 201480</td>
<td></td>
<td>1.07 [0.69;1.65]</td>
<td>1.64</td>
<td>[0.25;10.63]</td>
<td>0.58 [0.30;1.52]</td>
<td>0.92</td>
<td>[0.43;1.97]</td>
<td>2.09 [0.48;9.17]</td>
<td>0.82 [0.24;2.83]</td>
</tr>
<tr>
<td>Borst et al, 201481</td>
<td></td>
<td>1.28 [0.76;2.13]</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Albert et al, 201682</td>
<td></td>
<td>1.10 [0.86;1.41]</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alexander et al, 201681</td>
<td></td>
<td></td>
<td>-</td>
<td>2.18 [0.63;7.54]</td>
<td>-</td>
<td>2.17</td>
<td>[0.63;7.54]</td>
<td>-</td>
<td>2.18 [0.63;7.54]</td>
</tr>
<tr>
<td>Corona et al, 201875</td>
<td></td>
<td>1.02 [0.74;1.40]</td>
<td>0.97</td>
<td>[0.64;1.46]</td>
<td>0.84 [0.43;1.65]</td>
<td>0.79</td>
<td>[0.44;142]</td>
<td>-</td>
<td>0.99 [0.44;2.24]</td>
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</tbody>
</table>

### Erythrocytosis risk

<table>
<thead>
<tr>
<th>Meta-analyses considered</th>
<th>CV risk</th>
<th>Overall population</th>
<th>3.69 [1.82;7.51]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calof et al, 200577</td>
<td>Level of risk NA</td>
<td>Overall population</td>
<td>3.15 [1.56;6.35]</td>
</tr>
<tr>
<td>Fernandez-Balsells et al, 201079</td>
<td>Level of risk &gt; 50%</td>
<td>Overall population</td>
<td>3.62 [1.86;7.05]</td>
</tr>
<tr>
<td>Corona et al, 201585</td>
<td>Level of risk &gt; 52%</td>
<td>Overall population</td>
<td>4.89 [0.83;28.91]</td>
</tr>
<tr>
<td>Corona et al, (present study)</td>
<td>Level of risk &gt; 52%</td>
<td>Overall population</td>
<td>4.56 [2.64;7.89]</td>
</tr>
</tbody>
</table>

### Venous thromboembolism risk

<table>
<thead>
<tr>
<th>Meta-analyses considered</th>
<th>CV risk</th>
<th>Overall population</th>
<th>2.38 [0.26;21.62]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu et al, 201587</td>
<td>Level of risk</td>
<td>Overall population</td>
<td>1.96 [0.75;5.17]</td>
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<tr>
<td>Corona et al, 201585</td>
<td>Level of risk</td>
<td>RCTs</td>
<td>2.05 [0.78;5.39]</td>
</tr>
<tr>
<td>Houghton et al, 201888</td>
<td>Level of risk</td>
<td>Observational case control studies</td>
<td>1.34 [0.78;2.28]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort studies</td>
<td>4.89 [0.83;28.91]</td>
</tr>
<tr>
<td>Corona et al, (present study)</td>
<td>Level of risk &gt; 52%</td>
<td>Overall population</td>
<td>4.56 [2.64;7.89]</td>
</tr>
</tbody>
</table>

AMI = Acute myocardial infarction; CV = cardiovascular; MACE = major adverse cardiovascular event; NA = not available; RCTs = randomized controlled trials; T = testosterone.
cells) and indirect (stimulation of endogenous erythropoietin or inhibition of hepcidin, both involved in the iron pathway regulation) ones. Accordingly, available meta-analyses, which analyzed the risk of erythrocytosis due to TRT, in comparison with placebo, showed that T-treated subjects had a 3- to 4-fold increased risk of developing an elevated hematocrit. Old short-term parenteral T preparations have been reported to produce the highest risk of erythrocytosis, due to the high fluctuation of T levels. Accordingly, we previously reported that, when the analysis is limited to those studies applying transdermal preparations in the active arm and enrolling only subjects with hypogonadism (T < 12 nM), the risk of elevated hematocrit is not confirmed (Table 2). By using the data from the most updated meta-analysis on CV risk, we here confirm that when using either transdermal preparations or long-acting TU in subjects with hypogonadism (T < 12 nM), there is no increase in the risk of erythrocytosis (see also Table 2). This was not the case when older T ester preparations were considered, as previously reported (Table 2; 86).

Venous Thromboembolism Risk

Only few placebo-controlled RCTs have investigated a possible association between VTE risk and TRT. In 2015, Xu et al, by analyzing the data including only 3 RCTs enrolling 516 subjects, reported that TRT significantly increased VTE risk. These data were not confirmed by our group when 6 trials were considered, enrolling 1217 and 1,166 patients treated with TRT or placebo, respectively (88; Table 2). In line with this view, Houghton et al, by meta-analyzing placebo-controlled RCTs, including 2236 patients, and 5 observational studies, including 1,249,640 subjects, concluded that current evidence does not support an association between Tu and VTE (Table 2). Accordingly, it has been reported that TRT-related VTE events were frequently associated with an undiagnosed thrombophilia-hypofibrinolysis status, suggesting the relevance of an accurate medical history before starting TRT.

Prostate

The historical view that T is detrimental and harmful for prostate health is nowadays considered not to be evidence based. Several data have clarified that androgens not only are involved in the stimulation of prostate cell proliferation but also play a crucial role in the regulation of prostate cell differentiation. As support of the latter evidence, epidemiological data have shown that lower (ie, lower effect on prostate cell differentiation) rather than higher T circulating levels are associated with less differentiated forms of PC. In addition, it is important to recognize that in accordance with Morgentaler and Traish’s “satisfaction hypothesis,” during physiological conditions, circulating androgens saturate the human prostate androgen receptors making the prostate rather insensitive to further T increase. In line with their hypothesis, both in vitro and clinical evidence have documented that prostate cell proliferation is observed only

<table>
<thead>
<tr>
<th>Table 3. Odds ratio for prostate related events as derived from the available meta-analyses</th>
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<tbody>
<tr>
<td>Meta-analyses considered</td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Calof et al, 2005</td>
</tr>
<tr>
<td>Fernandez-Balsells et al</td>
</tr>
<tr>
<td>&amp; Cui and Zhang, 2013</td>
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<tr>
<td>Cui et al, 2013</td>
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<tr>
<td>Boyle et al, 2016</td>
</tr>
</tbody>
</table>

PSA = prostatic specific antigen.
at low T concentration levels but disappears when T levels reach the eugonadal range.\textsuperscript{39,90}

Several meta-analyses have been published specifically investigating the role of TRT on prostate safety (see also Table 3).\textsuperscript{77,79,92–96} The number of trials considered ranged from 4 to 26, including 1,084 to 5,464 subjects. In line with what has previously been reported, TRT induced only a short-term increase in prostatic specific antigen levels (95–65) or in prostate volume\textsuperscript{94} (Table 3). Conversely, when studies lasting more than 12 months were considered, no risk of PC or prostate-related events were reported (Table 3). Data from the T Trials confirm these observations, as no difference in prostate-related events or PC was observed when treated men were compared with those enrolled in the placebo group at the end point.\textsuperscript{50}

Similar data can be derived from registry studies. Data from the Registry of Hypogonadism in Men, a multinational registry of men with hypogonadism including 999 subjects (mean age 59.1 ± 10.5 years) with a follow-up of 3 years, did not document any difference in prostatic specific antigen levels, total International Prostate Symptom Score (IPSS) (including IPSS obstructive subscale), or PC in subjects undergoing TRT, when compared with those untreated.\textsuperscript{97} Interestingly, the same study also indicated that TRT resulted in even lower IPSS irritative subscale scores, when compared with untreated men.\textsuperscript{96} Similar results were derived from another Italian registry (SIAMO-NOI), which collected data from 432 men with hypogonadism in 15 centers.\textsuperscript{98} In addition, data derived from either animal models or clinical observations have documented that HG is characterized by an increased prostate inflammation, particularly evident in patients with obesity and metabolic disorders, which can contribute to benign prostatic hyperplasia-related symptoms and can be improved by TRT, explaining, at least partially, the aforementioned observations. Accordingly, preliminary data from a placebo-controlled RCT, involving 120 men with MetS and benign prostatic hyperplasia, showed that TRT produced a moderate improvement in lower urinary tract symptoms, associated with a significant decline in prostate artery flow velocity and acceleration, as assessed by transrectal color Doppler ultrasound, and with a decrease, in the prostatic tissue, of the expression of some inflammation-related genes, such as cyclooxygenase-2, monocyte chemotactic protein-1, and related orphan receptor gamma-\textsuperscript{t}.\textsuperscript{99}

A final point to be discussed is related to the effect of TRT in men treated for PC. A limited number of studies have investigated the role of TRT in men curatively treated after surgery with radiotherapy for PC. Recently, Telling et al\textsuperscript{100} collected and meta-analyzed information derived from 13 studies including 608 patients, of which 109 had a history of high-risk PC. The follow-up ranged from one to 189.3 months, and the type of T preparations used differed among studies. The authors concluded that TRT did not increase the risk of biochemical recurrence, but the available evidence is very low, limiting, therefore, the data interpretation.\textsuperscript{100}

**CONCLUSIONS**

Data derived from RCT and observational studies have clearly documented that TRT can improve erectile function, libido, and other aspects of sexual activities in men with hypogonadism (total T < 12 nmoles/L). The effect is inversely related to the baseline T levels and is lower in patients with higher numbers of associated morbidities. Although several data have documented that lower T levels are associated with a worse metabolic profile and a higher CV risk,\textsuperscript{101} the specific contribution of TRT in improving these aspects remains conflicting. In fact, whether the low T level in men with increased CV risk plays a direct role in the risk stratification or it represents an adaptive mechanism to a compromised health status has still not been completely clarified.\textsuperscript{53} Hence, based on the available evidence, TRT should not consider a viable alternative medication to improve metabolic profile in men with T2DM or MetS or to reduce the risk of bone fractures in men with osteoporosis. Similar considerations should be done for mood, cognition, and mobility.

When HG is correctly diagnosed and T is administered as per the recommended dosage, no CV risk is derived. However, it is important to recognize that the duration of the available trials is too short (lower than 3 years) to draw conclusions. In fact, limited information on possible long-term effects of TRT on CV risk is available. An industry-supported multicenter RCT is underway to investigate the long-term CV risk of TRT (clinicaltrials.gov: NCT03518034).

Similarly, the evidence published so far does not indicate any prostate risk related to TRT. However, none of the studies were sufficiently powered to exclude adverse event risks in the longer term. Similarly, preliminary positive data of TRT in IPSS improvement must be confirmed in well-designed long-term trials. In particular, limited information is available in men with severe lower urinary tract symptoms (ie, IPSS > 19) because they are usually excluded from RCTs.

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**STATEMENT OF AUTHORSHIP**

**Category 1**

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Giovanni Corona; Mario Maggi

(b) **Acquisition of Data**

Giovanni Corona

(c) **Analysis and Interpretation of Data**

Giovanni Corona; Mario Maggi
REFERENCES


SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jsxm.2019.11.270.