

# European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males

Endorsing organization: European Society of Endocrinology

Giovanni Corona<sup>1</sup>  | Dimitrios G. Goulis<sup>2</sup>  | Ilpo Huhtaniemi<sup>3,4</sup>  | Michael Zitzmann<sup>5</sup>  | Jorma Toppari<sup>4,6</sup>  | Gianni Forti<sup>7</sup> | Dirk Vanderschueren<sup>8</sup>  | Frederick C. Wu<sup>9</sup> 

<sup>1</sup>Endocrinology Unit, Medical Department, Azienda USL, Maggiore-Bellaria Hospital, Bologna, Italy

<sup>2</sup>Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

<sup>3</sup>Department of Metabolism, Digestion and Reproduction, Institute of Reproductive and Developmental Biology, Imperial College London, London, UK

<sup>4</sup>Institute of Biomedicine, Research Centre for Integrative Physiology and Pharmacology, University of Turku, Turku, Finland

<sup>5</sup>Institute of Reproductive Medicine, University Clinic Muenster, Muenster, Germany

<sup>6</sup>Department of Pediatrics, Turku University Hospital, Turku, Finland

<sup>7</sup>Endocrinology Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy

<sup>8</sup>Department of Endocrinology, University Hospitals Leuven, Leuven, Belgium

<sup>9</sup>Division of Endocrinology, Diabetes and Gastroenterology, School of Medical Sciences, University of Manchester, Manchester, UK

## Correspondence

Dirk Vanderschueren, Department of Endocrinology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.  
Email: dirk.vanderschueren@uzleuven.be

Frederick C. Wu, Division of Endocrinology, Diabetes & Gastroenterology, School of

## Abstract

**Background:** Evidence regarding functional hypogonadism, previously referred to as 'late-onset' hypogonadism, has increased substantially during the last 10 year.

**Objective:** To update the European Academy of Andrology (EAA) guidelines on functional hypogonadism.

**Methods:** Expert group of academicians appointed by the EAA generated a series of consensus recommendations according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system.

**Results:** The diagnosis of functional hypogonadism should be based on both the presence of clinical symptoms supported by repeatedly low morning fasting serum total testosterone (T) measured with a well-validated assay, after exclusion of organic causes of hypogonadism. Lifestyle changes and weight reduction should be the first approach in all overweight and obese men. Whenever possible, withdrawal/modification of drugs potentially interfering with T production should be advised. Testosterone replacement therapy (TRT) is contraindicated in men with untreated prostate or breast cancer, as well as severe heart failure. Severe low urinary tract symptoms and haematocrit >48%-50% represent relative contraindications for TRT. Prostate-specific antigen and digital rectal examination of the prostate should be undertaken in men >40 years of age before initiating TRT to exclude occult prostate cancer. Transdermal T should be preferred for initiation of TRT, whereas gonadotrophin therapy is only recommended when fertility is desired in men with secondary hypogonadism. TRT is able to improve sexual function in hypogonadal men. Other potential positive outcomes of TRT remain uncertain and controversial.

**Conclusion:** TRT can reliably improve global sexual function in men with hypogonadism in the short term. Long-term clinical benefits, and safety of TRT in functional hypogonadism, remain to be fully documented. Clinicians should therefore explicitly discuss the uncertainties and benefits of TRT and engage them in shared management decision-making.

[Corrections added on 15 May 2020 after first online publication: Endorsing organization: European Society of Endocrinology has been moved from the footnote to the article byline].

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Medical Sciences, University of Manchester,  
Manchester, UK.  
Email: frederick.wu@manchester.ac.uk

## KEYWORDS

cardiovascular risk, erectile dysfunction, functional hypogonadism, late-onset hypogonadism, libido, obesity, testosterone

## 1 | INTRODUCTION

The last guidelines on male late-onset hypogonadism (LOH—now more appropriately referred to as functional hypogonadism) from the European Academy of Andrology (EAA) have been published 10 years ago in collaboration with several other international societies.<sup>1</sup> More recently, our understanding of underlying mechanisms of functional hypogonadism as well as of pros and cons of testosterone (T) replacement therapy (TRT) has improved. Comorbidities, obesity and the metabolic syndrome (MetS), amongst other causes (see later), may contribute independently to individual rates and extent of the apparent age-related decline of T observed in middle-aged and elderly men.<sup>2,3</sup> Thus, the emergent condition of functional hypogonadism, in contradistinction to the organic or classical hypogonadism, is gaining credence as a defined clinical entity and diagnosis.<sup>4</sup> According to Grossmann and Matsumoto,<sup>4</sup> functional hypogonadism (also referred to as late-onset, age-related or adult-onset hypogonadism) is defined as the coexistence of androgen deficiency-like features and low serum T concentrations occurring in the absence of both intrinsic structural hypothalamic-pituitary-testis (HPT) axis pathology and of specific pathologic conditions suppressing the HPT axis (such as microprolactinoma, endogenous Cushing syndrome) in middle-aged or older men. The community prevalence estimates of potentially functional hypogonadism in middle-aged and older men vary from 2.1% to 12.3%.<sup>4</sup> Functional hypogonadism may be potentially reversible if the underlying causes are identified and adequately treated or removed, whereas organic hypogonadism is generally an irreversible condition secondary to genetic faults or pathological perturbations of the HPT axis.<sup>4</sup> The EAA largely agrees with the guidelines of the United States (US) Endocrine Society<sup>5</sup> on the diagnosis and treatment of organic or classical hypogonadism.

The Testosterone trials (TTrials), a coordinated set of seven placebo-controlled randomized clinical trials (RCTs), recently provided evidence of moderate efficacy of TRT for 12 months in a variety of clinical endpoints in elderly men with functional hypogonadism.<sup>6</sup> The EAA recognizes that longer-term patient-important clinical benefits and potential adverse effects of TRT in older men remain controversial.<sup>7</sup> This latter is further highlighted by potential safety concerns, raised in the US, with respect to increased cardiovascular (CV) risks associated with the prescription of T in older men.<sup>7</sup>

The aim of the present paper is to provide a European perspective, based largely on high-quality RCTs and meta-analyses, on late-onset/functional (rather than classical/organic) hypogonadism. In this respect, only adult hypogonadism, including fertility issues, will be considered

## SUMMARY OF RECOMMENDATIONS

**Recommendation #01.** We recommend the diagnosis of functional hypogonadism only on the basis of the presence of clinical symptoms or signs of T deficiency in combination with consistently low morning serum T concentrations (1⊕⊕⊕○) (see also recommendation #04).

**Recommendation #02.** We recommend against universal screening for hypogonadism in middle-aged or older men, by structured interviews or questionnaires and/or random total T measurements (1⊕⊕○○).

**Recommendation #03.** We recommend that the clinical diagnosis of functional hypogonadism should be confirmed by measurement of serum total T with a well-validated assay on fasting morning (before 11 AM) blood samples obtained on two different days (1⊕⊕⊕○).

**Recommendation #04.** Functional hypogonadism should be diagnosed only after exclusion of organic causes of hypogonadism. In addition, to morning total T, luteinizing hormone (LH) should be measured in all patients with suspected functional hypogonadism to differentiate between the primary and secondary causes (1⊕⊕⊕○).

**Recommendation #05.** We recommend either measuring or calculating free T (fT), in addition to total T, in patients with conditions that alter sex hormone-binding globulin (SHBG) and when total T concentrations are in the borderline range (~8–12 nmol/L) if the clinical suspicion of hypogonadism is strong (1⊕⊕⊕○).

**Recommendation #06.** We recommend lifestyle changes, including physical exercise and weight reduction, in overweight and obese men with functional hypogonadism since weight loss may increase T concentrations (1⊕⊕⊕○).

**Recommendation #07.** We suggest withdrawal/modification of drugs (eg opiates, anabolic steroids, glucocorticoids) potentially interfering with T production, when clinically permissible (2⊕⊕⊕○).

**Recommendation #08.** We suggest the use of transdermal T, as the preferred preparation in the initiation of TRT for functional hypogonadism (2⊕⊕○○).

**Recommendation #09.** We recommend gonadotrophin therapy in men with secondary hypogonadism only when fertility is desired (1⊕⊕⊕⊕).

**Recommendation #10.** We recommend TRT in hypogonadal men with sexual/erectile dysfunction(ED) to improve libido, erectile function and sexual satisfaction (1⊕⊕⊕⊕).

**Recommendation #11.** We recommend against TRT as a treatment for weight reduction in obese men (1⊕⊕○○).

**Recommendation #12.** We recommend against TRT to improve glycometabolic control in men with type 2 diabetes (T2DM) and/or metabolic syndrome (MetS) (1⊕⊕○○).

**Recommendation #13.** We recommend against TRT for the sole purpose of reducing fracture risk in hypogonadal men with high fracture risk (1⊕⊕⊕○).

**Recommendation #14.** We recommend against TRT for the sole treatment to improve depressive symptoms in hypogonadal men (1⊕⊕○○).

**Recommendation #15.** We recommend against the use of TRT, in the absence of symptomatic hypogonadism, to improve morbidity and/or mortality of several chronic diseases including human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS), heart failure, obstructive pulmonary disease, chronic kidney diseases, bowel inflammatory diseases or to prevent the long-term outcomes of subjects chronically treated with glucocorticoid or opioid therapy (2⊕⊕○○).

**Recommendation #16.** We recommend against routinely prescribing T to men >65 years as an anti-ageing therapy (1⊕⊕⊕⊕).

**Recommendation #17.** We recommend against TRT in frail men to improve exercise capacity/physical function (1⊕⊕⊕○).

**Recommendation #18.** We recommend against TRT in ageing men to improve cognitive function (1⊕⊕⊕○).

**Recommendation #19.** We recommend against TRT in men with untreated prostate or breast cancer (Good Clinical Practice statement).

**Recommendation #20.** We recommend, before initiation of TRT in men >40 years of age, discussing potential benefits and risks of prostate cancer screening and engaging the patient in shared decision-making regarding options for pre-treatment screening and on-treatment monitoring (see *Recommendations #21, #22, #31, #32*). These discussions should also take into account local guidelines for prostate cancer screening for the general population (Good Clinical Practice statement).

**Recommendation #21.** We recommend, before initiation of TRT in men >40 years of age, checking prostate-specific antigen (PSA) and performing digital rectal examination (DRE) of the prostate in order to minimize the risk of prescribing T to patients with undiagnosed prostate cancer(1⊕⊕○○).

**Recommendation #22.** We recommend against TRT in men with PSA > 4 ng/mL (or elevated PSA according to local/

national guidelines) or prostate abnormalities on DRE without further evaluation and/or urological consultation (1⊕⊕○○).

**Recommendation #23.** We suggest that TRT should not be used in men with severe lower urinary tract symptoms (LUTS) [International Prostate Symptom Score (IPPS) >19] (2⊕○○○).

**Recommendation #24.** We recommend against TRT in men with severe heart failure [New York Heart Association (NYHA) Class III or IV] (1⊕⊕○○).

**Recommendation #25.** We suggest against TRT in patients with a recent major acute CV event (including stroke) (2⊕⊕○○).

**Recommendation #26.** We suggest against TRT in men with documented polycythaemia and/or elevated haematocrit (>48%-50%) depending on CV risk and associated morbidities without further evaluation (2⊕⊕○○).

**Recommendation #27.** We suggest obtaining a detailed personal and family history of venous thromboembolism (VTE) and risk factors for VTE prior to initiating TRT (2⊕○○○).

**Recommendation #28.** We recommend against TRT in hypogonadal men who desire fertility (1⊕⊕⊕⊕).

**Recommendation #29.** We recommend assessing the clinical response as well as adverse effects to TRT at 3 and 12 months after initiation of treatment. Thereafter, clinical review should be scheduled at least yearly (1⊕⊕⊕⊕).

**Recommendation #30.** We suggest that on-treatment serum total T concentrations should be measured at each clinic visit to ensure that average total T concentrations achieve the targeted mid-normal range for young men (2⊕⊕○○).

**Recommendation #31.** We suggest performing digital rectal examination and checking PSA at 3 to 12 months for men >40 years of age after initiating T treatment. After the first 12 months, local guidelines for prostate cancer screening for the general population should be followed (2⊕○○○).

**Recommendation #32.** We suggest further evaluation and/or urological consultation if there is: (a) an increase in serum PSA concentration > 1.4 ng/mL within 12 months of initiating T treatment, (b) a confirmed PSA > 4 ng/ml at any time and (c) detection of a prostatic abnormality on DRE or a substantial worsening of LUTS(2⊕○○○).

**Recommendation #33.** We recommend measuring the haematocrit (Hct) 3-6 months after initiation of TRT and then annually. If Hct is >54%, TRT should be discontinued until Hct decreases to a safe level; evaluate the patient for hypoxia and sleep apnoea; consider reinitiating TRT with a reduced dose(1⊕⊕⊕⊕).

in the present guidelines. Delayed puberty and induction of secondary sexual development in adolescent patients will not be included.

## 2 | METHODS

The EAA guidelines committee commissioned an expert task force of academicians to update the previous guidelines on LOH published in 2009.<sup>1</sup>

Following scrutiny and discussion of the best evidence from published literature available in PubMed, the authors, comprising an expert group of academicians appointed by the EAA, generated a series of consensus recommendations according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system.<sup>8</sup> In particular, according to GRADE, the number '1' denotes a strong recommendation and is expressed with the phrase 'we recommend', whereas the number '2' denotes a weaker recommendation and it is expressed with the phrase 'we suggest'. The quality of evidence is expressed through graphical descriptions: ⊕○○○ denotes 'very low-quality evidence', ⊕⊕○○ 'low quality', ⊕⊕⊕○ 'moderate quality' and ⊕⊕⊕⊕ 'high quality'.

### 2.1 | Diagnosis

#### 2.1.1 | Recommendations

**Recommendation #01:** We recommend the diagnosis of functional hypogonadism only on the basis of the presence of clinical symptoms and signs of T deficiency in combination with consistently low morning serum T concentrations (1 ⊕⊕⊕○) (see also *recommendation #04*).

**Recommendation #02:** We recommend against universal screening for hypogonadism in middle-aged or older men, by structured interviews or questionnaires and/or random total T measurement (1 ⊕⊕○○).

**TABLE 1** Symptoms and signs that may be associated with functional hypogonadism

Specific symptoms
<ul style="list-style-type: none"> <li>• Reduced libido</li> <li>• Decreased spontaneous erections</li> <li>• Erectile dysfunction</li> </ul>
Less specific symptoms
<ul style="list-style-type: none"> <li>• Decreased energy</li> <li>• Decreased physical strength/function/activity</li> <li>• Decreased motivation</li> <li>• Low mood</li> <li>• Decreased concentration</li> <li>• Hot flushes</li> </ul>
Less specific signs
<ul style="list-style-type: none"> <li>• Loss of body/facial hair</li> <li>• Decreased testicular volume</li> <li>• Increased body fat/reduced muscle mass</li> <li>• Osteoporosis/low bone density</li> <li>• Central obesity</li> </ul>

#### 2.1.2 | Evidence

Functional hypogonadism may present with clinical symptoms or signs similar to classical hypogonadism (Table 1). Unlike classical hypogonadism, functional hypogonadism usually presents a more subtle clinical picture, with non-specific symptoms and usually no overt signs of androgen deficiency. Furthermore, these symptoms often overlap with those arising from co-existing co-morbidities and the effects of ageing in older men.<sup>9</sup> Nevertheless, sexual complaints, such as decreased libido, morning erections or erectile dysfunction (ED), were more frequently associated with low T in community-dwelling middle-aged and elderly European men.<sup>10</sup> Similar results were confirmed in a large cohort of patients presenting to a specialized sexual medicine clinic with ED.<sup>11</sup> In contrast, psychological or physical symptoms/signs were not significantly associated with low T concentrations.<sup>10,11</sup>

Obesity and in particular central obesity are frequently associated with functional hypogonadism, which is potentially reversible, for instance, following weight reduction.<sup>12</sup> Conversely, other clinical signs typically associated with classical hypogonadism, such as reduced testis volume, are less common (1).

#### 2.1.3 | Values

For the clinical diagnosis of hypogonadism, we place a higher value on the presence and severity of sexual symptoms, particularly low libido and lower values on more non-specific symptoms such as lack of energy/fatigue, poor memory/concentration or decreased physical strength/function/mobility (Figure 1).

We also highly value the recognition of obesity of all grades, but particularly World Health Organization (WHO) class III, as a major and increasingly common cause of low T (total T—see later) in middle-aged and elderly men, since this is reversible after weight reduction, consequently also bringing multiple additional health benefits.

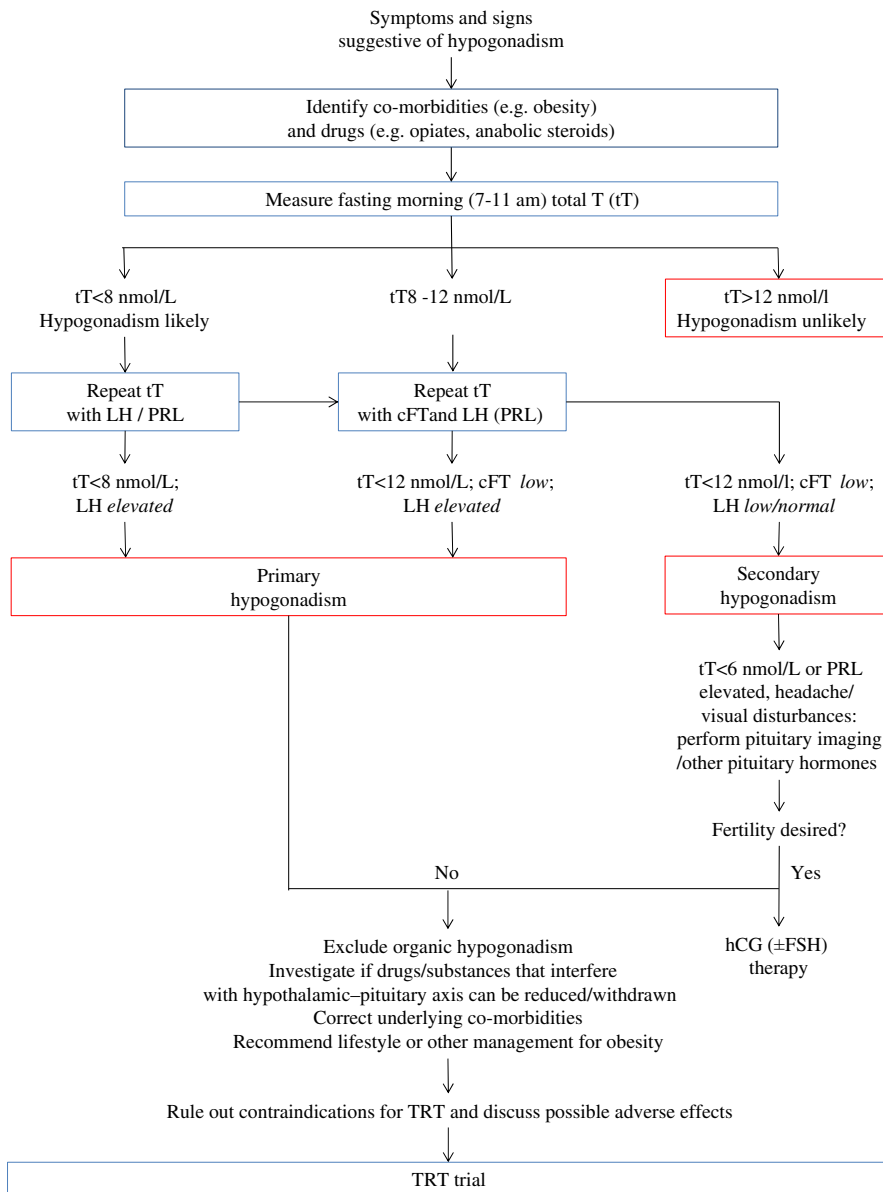
#### 2.1.4 | Remarks

Self-reported questionnaire or structured interviews have poor specificity and should not be used for population screening of hypogonadism. It remains important to regularly reassess the diagnosis of functional hypogonadism, especially in the presence of reversible conditions (see below) that may temporarily lower T.

### 2.2 | T measurements

#### 2.2.1 | Recommendations

**Recommendation #03:** We recommend that the clinical diagnosis of functional hypogonadism should be confirmed by



**FIGURE 1** Proposed flow chart to correctly diagnose and manage functional hypogonadism. cFT, calculated free testosterone; FSH, follicular-stimulating hormone; hCG, human chorionic gonadotrophin; LH, luteinizing hormone; PRL, prolactin; T, testosterone; TRT, testosterone replacement therapy

measurement of serum total T with a well-validated assay on fasting morning (before 11 AM) blood samples obtained on two different days (1 ⊕ ⊕ ⊕ ⊕).

## 2.2.2 | Evidence

T concentrations show significant diurnal as well as considerable day to day intra-individual variation in men.<sup>13</sup> T concentrations may also be temporarily decreased during acute illness or due to medication use.<sup>14</sup> Moreover, T may be lowered following ingestion of glucose or food.<sup>15</sup>

The most accurate and precise method for determination of T concentrations is liquid chromatography-tandem mass spectrometry (LC-MS/MS). However, this preferred method of choice is not universally available (due to financial and technical constraints) at present. Most laboratories continue to employ automated platform T immunoassays, which, if well-standardized, can show high

correlation with LC-MS/MS within the adult male T range although they offer less precision in the hypogonadal range.<sup>16</sup>

The exact T concentration below which a diagnosis of functional hypogonadism can be confidently made remains elusive and controversial. Recently, T concentrations in healthy men were harmonized internationally between several large population cohorts in the US and Europe using a reference LC-MS/MS method.<sup>17</sup> The harmonized lower limits of the reference range for T in healthy, non-obese young men (aged 19-39 years) were 9.2 nmol/L (264 ng/dL) and 10.5 nmol/L (303 ng/dL) using, respectively, the 2.5th and 5th percentiles.<sup>17</sup> In the European Male Ageing Study (EMAS) (men aged 40-79 years), higher prevalence of sexual symptoms (poor morning erections, decreased libido, and ED) was associated with T concentrations <11 nmol/L (<320 ng/dL) after adjustment for age.<sup>10</sup> Available evidence derived from meta-analyses suggests less benefits of TRT in subjects with total T > 12 nmol/L (>350 ng/dL) and higher efficacy in patients with lowest T (T < 8 nmol/L; <231 ng/dL; Refs. [18,19]; see below).

Hence, there appears to be some degree of consistency pointing to the lower limit of normality of T concentrations being in the range of 8–12 nmol/L (231–350 ng/dL).

### 2.2.3 | Values

To minimize the above-mentioned biological variability in circulating T concentration in order to improve diagnostic precision, we place a high value in recommending that T should be measured in the fasting state between 7 and 11 AM on at least two different days. In addition, measurement of T during acute illness should be avoided.

Hypogonadism is highly unlikely with T values >12 nmol/L (>350 ng/dL; Figure 1) but more likely in patients with T concentrations consistently <8 nmol/L (<231 ng/dL). The lower the T concentration below the lower limit of the reference range, the higher is the likelihood that symptoms will be explained by testosterone deficiency. In those patients with borderline T concentrations between 8–12 nmol/L (231–350 ng/dL), a clear diagnosis cannot be confidently established, but free T (fT) measurements can often be helpful in this situation (see Section 6).

### 2.2.4 | Remarks

Due to significant inter-laboratory variations in T measurements, clinicians and clinical biochemists should ensure that their laboratories measure T concentrations with a reliable assay (either LC-MS/MS or immunoassay), that is regularly standardized by an accuracy-based (rather than peer-based) external quality assurance scheme, preferably calibrated against an internationally harmonized reference range.<sup>17</sup> Clinicians have a duty to seek assurance on the best quality of T results from their laboratories and demand improvements if necessary. Individual T results should be interpreted against a reference range established by regional laboratories in healthy men from a representative local general population. Although T concentrations decline with age,<sup>10</sup> there is currently insufficient evidence from prospective population data or clinical experience to support the use of an age-stratified reference interval (Z-score approach) for T, as suggested by the Endocrine Society of Australia.<sup>20</sup>

## 2.3 | Differential diagnosis

### 2.3.1 | Recommendations

**Recommendation #04:** Functional hypogonadism should be diagnosed only after exclusion of organic causes of hypogonadism. In addition to morning total T, luteinizing hormone (LH) should be measured in all patients with suspected functional hypogonadism to differentiate the primary from secondary causes (1⊕⊕⊕○).

### 2.3.2 | Evidence

The differential diagnosis between primary and secondary hypogonadism is essential for functional as well as classical hypogonadism. Most cases of functional hypogonadism have secondary or mixed hypogonadism with low to normal luteinizing hormone (LH; Table 2). Primary hypogonadism with elevated LH and even more follicle-stimulating hormone (FSH) indicating testicular failure is more commonly related to classical hypogonadism (Figure 1). However, functional testicular failure is possible in the elderly (>70 years), especially in association with co-morbidities.<sup>21</sup> Conversely, co-morbidities, and obesity in particular, are frequently associated with secondary hypogonadism.<sup>21</sup>

### 2.3.3 | Remarks

If organic secondary hypogonadism is suspected, further investigations should include magnetic resonance imaging (MRI) scanning of the pituitary-hypothalamus, iron saturation and prolactin measurement as well as determination of other pituitary hormones. The overall cost-effectiveness of MRI scanning (finding major lesions that requires intervention), in the absence of clinical evidence of pituitary mass effects such as visual disturbances, headache or hyperprolactinaemia, is relatively low, but should be considered when T concentrations are <6 nmol/L (<175 ng/dL) (Refs. [22,23]; Figure 1). However, it is important to recognize that underlying causes (potentially reversible or treatable) are often not identifiable in subjects with functional hypogonadism, and it may not always be possible to completely exclude occult organic abnormalities, even after appropriate investigations.

## 2.4 | Role of fT

### 2.4.1 | Recommendations

**Recommendation #05:** We recommend either measuring or calculating fT, in addition to total T, in patients with conditions that alter sex hormone-binding globulin (SHBG), and when total T concentrations are in the borderline range (8–12 nmol/L; 231–350 ng/dL), if the clinical suspicion of hypogonadism is strong (Table 3; 1⊕⊕⊕○).

### 2.4.2 | Evidence

Several clinical conditions and medications (Table 3) can substantially modify SHBG concentration, contributing to difficulties in interpreting total T results. Obesity, for instance, is frequently associated with insulin resistance, low SHBG concentration and hence low total T (but fT remains normal); this may spuriously lead to a diagnosis of functional hypogonadism in many symptomatic obese men (see below).<sup>24</sup> Recent data indicate that in obese men with apparent functional secondary hypogonadism, a decrease



**TABLE 2** Causes of hypogonadism

Primary hypogonadism
Organic or classical
<ul style="list-style-type: none"> <li>• Congenital: anorchia, Klinefelter syndrome and other chromosomal abnormalities, myotonic dystrophy, defects of testosterone biosynthesis, disorders of sex differentiation (gonadal dysgenesis), cryptorchidism</li> <li>• Acquired: varicocele, trauma, torsion, surgery, chemotherapy, irradiation, orchitis</li> </ul>
Functional
<ul style="list-style-type: none"> <li>• Ageing</li> <li>• Drug-induced: ketoconazole, aminoglutethimide, mitotane, metyrapone</li> <li>• Chronic systemic diseases</li> <li>• Organ failure</li> <li>• Glucocorticoid excess: iatrogenic, Cushing syndrome</li> <li>• Alcohol abuse</li> </ul>
Secondary hypogonadism
Organic or classical
<ul style="list-style-type: none"> <li>• Congenital: Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, Rathke's cleft cyst, haemochromatosis</li> <li>• Acquired: Traumatic brain injury, cranial or pituitary irradiation/surgery, pituitary adenomas, hypothalamic tumours (eg craniopharyngiomas, germinomas and other germ tumours), pituitary stalk diseases, inflammatory and infectious diseases (eg lymphocytic hypophysitis, infections, granulomatous lesions, sarcoidosis, Langerhans' histiocytosis), iron excess</li> </ul>
Functional
<ul style="list-style-type: none"> <li>• Acute or critical illness</li> <li>• Drug-induced: opioids, glucocorticoids, androgens/ anabolic-androgenic steroids, GnRH analogues, cyproterone acetate, psychotropic drugs causing hyperprolactinaemia</li> <li>• Malnutrition, excessive exercise</li> <li>• HIV/AIDS</li> <li>• Cannabinoid abuse</li> <li>• Obesity, T2DM, co-morbidities, sleep apnoea</li> </ul>
Androgen resistance/decreased testosterone bioactivity
Organic or classical
<ul style="list-style-type: none"> <li>• Congenital: Aromatase deficiency, Kennedy disease, partial or complete androgen insensitivity, 5<math>\alpha</math>-reductase type II deficiency, 17<math>\beta</math>-hydroxysteroid dehydrogenase III deficiency</li> </ul>
Functional
<ul style="list-style-type: none"> <li>• Drug-induced AR blockade: steroidal anti-androgen (eg cyproterone acetate, spironolactone), non-steroidal anti-androgen (eg flutamide, bicalutamide, nilutamide)</li> <li>• Drug-induced 5<math>\alpha</math>-reductase activity blockade: finasteride, dutasteride</li> <li>• Increased SHBG</li> </ul>

Abbreviations: AIDS, acquired immunodeficiency syndrome; AR, androgen receptor; GnRH, gonadotrophin-releasing hormone; ER, oestrogen receptor; HIV, human immunodeficiency virus; SHBG, sex hormone-binding globulin; T2DM, type 2 diabetes.

of total T is only associated with hypogonadal symptoms, when fT is also low.<sup>25-27</sup> Conversely, elevated SHBG (eg human immunodeficiency virus, HIV; liver disease and old age) may lead to high or normal total T, potentially masking the diagnosis of hypogonadism.<sup>24-27</sup>

## 2.4.3 | Values

We place a high value on the additional information offered by fT when SHBG is altered, or when T results are in the borderline range 8-12 nmol/L (231-350 ng/dL), especially when clinical suspicion of hypogonadism is strong (Figure 1).

## 2.4.4 | Remarks

Direct analogue assays are unreliable for the evaluations of fT concentrations and should not be used.<sup>28</sup> Measurement of fT by equilibrium dialysis (EqD) remains the most accurate and should ideally be the method of choice.<sup>28,29</sup> However, EqD is technically difficult, expensive and seldom available to physicians. A pragmatic alternative, therefore, is to use calculated fT, with formulae or algorithms based on the binding characteristics of SHBG, and albumin to T. Different calculation methods for estimation of fT concentrations on the basis of total T, SHBG and albumin are available, but the best choice remains controversial.<sup>28</sup> In a recent comparison between calculated and EqD-measured fT, the Vermeulen method,<sup>30</sup> based on the law of mass action equations appeared to be the most consistent albeit with a small but systematic overestimation.<sup>29</sup> It is important to point out that reference ranges for fT (whether directly measured or calculated) have not been validated prospectively in relation to incident outcomes and in RCTs. Only few studies have attempted to correlate fT thresholds with higher prevalence of sexual and physical dysfunctions.<sup>10,11</sup> fT concentrations < 220 pmol/L (<6.3 ng/dL), with a range of 170-240 pmol/L (5.0-7.0 ng/dL), have been suggested to be compatible with a symptomatic androgen deficiency state.<sup>10,11,31-36</sup> Further standardization as well as validation of fT as a definitive marker of hypogonadism is an important task for clinical research in the near future.

**TABLE 3** Conditions that may alter serum SHBG and thereby total T concentrations

Decreased SHBG
<ul style="list-style-type: none"> <li>• Obesity</li> <li>• Glucocorticoids</li> <li>• Androgenic and progestogenic steroids</li> <li>• Nephrotic syndrome</li> <li>• Hypothyroidism</li> <li>• Acromegaly</li> <li>• Polymorphisms in the SHBG gene</li> </ul>
Increased SHBG concentrations
<ul style="list-style-type: none"> <li>• Ageing</li> <li>• AIDS/HIV disease</li> <li>• Cirrhosis and hepatitis</li> <li>• Hyperthyroidism</li> <li>• Anticonvulsants</li> <li>• Oestrogens</li> <li>• Polymorphisms in the SHBG gene</li> </ul>

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; SHBG, sex hormone-binding globulin; T, testosterone.

Adapted from Bhasin et al.<sup>5,83</sup>

### 3 | TREATMENT

#### 3.1 | Lifestyle and concomitant medications

##### 3.1.1 | Recommendations

**Recommendation #06.** We recommend lifestyle changes, including physical exercise and weight reduction, in overweight and obese men with functional hypogonadism since weight loss may increase T concentrations (1⊕⊕⊕○).

**Recommendation #07.** We suggest withdrawal/modification of drugs (eg opiates, anabolic steroids and glucocorticoids) potentially interfering with T production, when clinically permissible (2⊕⊕⊕○).

##### 3.1.2 | Evidence

Longitudinal data from the EMAS clearly documented that obesity at the baseline and weight gain during the follow-up increased the risk of developing functional secondary hypogonadism. In men who lost weight during follow-up, in contrast, T often increased with recovery from secondary hypogonadism.<sup>37,38</sup> A meta-analysis of available evidence confirmed that weight loss (obtained by either low-calorie diet or bariatric surgery) improves T concentrations proportionately to the weight loss obtained.<sup>12,39</sup> Similar results have also been reported for physical activity.<sup>39</sup> The mechanisms underlying such functional alterations in the HPT axis have not been completely clarified. However, it is plausible that metabolic disturbances and inflammatory states associated with obesity can directly interfere with T/gonadotrophin secretion at multiple levels.<sup>24,40</sup>

Several drugs may inhibit HPT axis function and impair T production. Other drugs may interfere with androgen receptor-mediated action in target tissues (1). Opioid treatment in men with chronic non-cancer pain (CNCP) is one of the most frequently encountered examples of drug-induced functional hypogonadism.<sup>41,42</sup> Opioid medication withdrawal usually normalizes T concentrations within 1 month.<sup>41</sup> The abuse of anabolic-androgenic steroids (AAS) and, in particular, their withdrawal after long-term use represents another increasingly serious issue, which may not always be immediately apparent unless there is a high level of suspicion and awareness by the clinician.<sup>43</sup> Patients should be informed and reassured that the overwhelming majority of AAS abusers will eventually recover normal gonadal function (may take more than 12 months after prolonged abuse) provided they comply with full abstinence. Clomiphene or human chorionic gonadotrophin (hCG) (attempting to hasten recovery) should not be used, as there is insufficient evidence of efficacy.

##### 3.1.3 | Values

Weight reduction should be the first line of management and strongly encouraged in all overweight and obese men with low T. Significant collateral health benefits may also accrue from these

lifestyle changes, potentially offering valuable opportunities for preventative care in middle-aged men. When drugs (prescribed as well as off-label) interfering with HPT axis are identified as the cause of functional hypogonadism, the possible benefit/risk ratio of their withdrawal/modification should be discussed with the patient as well as their primary care physician.

#### 3.2 | Testosterone treatments

##### 3.2.1 | Recommendations

**Recommendation #08.** We suggest the use of transdermal T, as the preferred preparation in the initiation of TRT for functional hypogonadism (2⊕⊕○○).

##### 3.2.2 | Evidence

Several T preparations are available for oral, transdermal and parenteral administration (Rastrelli et al,<sup>44</sup>). Oral T undecanoate (TU) is no longer considered a viable therapeutic option, since its absorption is unpredictable and highly dependent on food intake (Rastrelli et al,<sup>44</sup>). The older T injectable formulations, such as T propionate and enanthate or T ester combinations, may cause wide fluctuations in serum T concentrations, frequently reported as unpleasant mood/energy swings by patients and possibly associated with increased risk of polycythaemia.<sup>44</sup> Nasal preparations, which may cause irritation of nasal mucosa, are not currently available in Europe.<sup>44</sup> T pellet implants, not available in European countries except the UK, require a minor surgical procedure with the risk of extrusion or infections. Presently, long-acting injectable TU and T gels are the most frequently prescribed and acceptable T preparations.<sup>44</sup> TRT for functional hypogonadism is often commenced as a therapeutic trial since the causal relationship between symptoms of hypogonadism, and low T is not always certain at start of treatment. Therefore, a short-acting preparation such as T gel rather than a long-acting depot injection may be more appropriate. Many clinicians also prefer starting TRT with T gel, due to the potentially reversible nature of functional hypogonadism with the need to reassess the patient after treatment interruption. In frail elderly patients with multiple morbidities, in whom the risks of adverse effects are higher, a short-acting gel T preparation at a lower starting dose is advisable.

We, therefore, suggest initiating TRT with a T gel for a period of three to six months in men considered to have functional hypogonadism. The TTrial<sup>6</sup> clearly showed improvement of most symptoms within three months following initiation of T gel treatment and recovery of T concentrations to the mid-normal range. If there is no clinical improvement after six months of sufficient T replacement, TRT should be discontinued and other causes of symptoms or alternate T modalities considered if therapeutic T concentrations have not been consistently achieved (Figure 1). If the patient shows significant clinical benefits, switching to longer-acting T preparations of TRT could



be discussed. It is important for clinicians to discuss frankly with their patients the uncertain risks and benefits of TRT in functional hypogonadism, as well as the pros and cons of available T preparations, in a process of shared decision-making on management choices.<sup>45</sup>

### 3.2.3 | Values

Due to the potentially reversible nature of functional hypogonadism, we prefer to initiate TRT with short-acting T gel preparations, particularly in older subjects with co-morbidities.

### 3.2.4 | Remarks

The most important side effect of T gel treatment is the possibility to cross-transfer T to others during contact with the skin's surface. In order to limit this possibility, a higher T concentration preparation (1.6%–2.0%) may be preferred.<sup>44</sup> This modification may allow a reduced amount of gel applied, thereby limiting the transfer risk.<sup>44</sup> A common problem with T gel is the variable transdermal absorption of T resulting in changing T concentrations from day to day. Regular monitoring of on-treatment T concentrations and dosage adjustments is, therefore, advisable. Similar to gels, the long-acting injectable TU has shown a good benefit/safety profile.<sup>44</sup> However, in case of side effects, rapid T withdrawal is not possible.<sup>44</sup> In addition, coughing as a potential sign of pulmonary oil microembolism has been observed following the intramuscular injections of long-acting TU and other esters.<sup>44</sup>

## 3.3 | Gonadotrophin treatment

### 3.3.1 | Recommendations

**Recommendation #09.** We recommend gonadotrophin therapy in men with secondary hypogonadism only when fertility is desired (1⊕⊕⊕⊕).

### 3.3.2 | Evidence

Testicular function is intact in functional secondary hypogonadism and should respond to exogenous gonadotrophin stimulation. The most widely used preparation is hCG. One meta-analysis on gonadotrophin treatment in patients with organic secondary hypogonadism, showed an overall successful outcome (defined as the appearance of at least one spermatozoon in the semen) in 75% of patients, with a mean sperm concentration achieved of 6 million/mL.<sup>46</sup> The same study showed that combined therapy with FSH and hCG was associated with a better outcome in patients with *organic* secondary hypogonadism.<sup>46</sup> Similar data on pregnancy outcomes following combined treatment with hCG and FSH in functional hypogonadism are not available.

### 3.3.3 | Values

In patients with functional secondary hypogonadism who desire fertility, in whom treatment is contraindicated (suppression of spermatogenesis—vide infra), we put a higher value on gonadotrophin (hCG) treatment and less emphasis on the current lack of outcome data. The place of FSH treatment in functional secondary hypogonadism has not been assessed. After fertility has been achieved, TRT may be reinitiated.

### 3.3.4 | Remarks

As alternatives to T, oestrogen receptor blockers (anti-oestrogens, eg clomiphene, tamoxifen, enclomiphene) or aromatase inhibitors (eg letrozole) have been suggested as off-label treatment to maintain fertility and restore hypogonadism-related symptoms in subjects with functional hypogonadism. However, the available evidence is poor due to limited number of RCTs, inadequate outcome data, short duration of the trials as well as small numbers of subjects enrolled.<sup>47</sup>

## 4 | TREATMENT OUTCOMES

The best evidence on outcomes of TRT in older men with functional hypogonadism comes from the recent TTrialS. These studies comprised a set of seven placebo-controlled RCTs enrolling 788 symptomatic hypogonadal men > 65 years (mean age 72 years) with unequivocally low T of <9.4 nmol/L (<275 ng/dL) [mean baseline T 8.1 nmol/L (233 ng/dL)] in a 12-month study using T gel 5mg daily as the active treatment.<sup>6</sup> This contrasted with other available RCTs which often included a combination of both hypogonadal and eugonadal men—a crucial limitation.

Meta-analyses are often considered the gold standard for the evaluation of the efficacy of a specific treatment and particularly useful to address questions for which multiple data sources are conflicting. However, meta-analyses on various TRT outcomes of placebo-controlled RTCs in men with functional hypogonadism have been marred by significant heterogeneity, low study quality, small participant numbers as well as short duration in the studies included,<sup>7,44</sup> thereby devaluing the conclusions therefrom. Data derived from observational and uncontrolled studies on TRT are plentiful, but level of evidence in these studies is poor and therefore not taken into account in these guidelines.

### 4.1 | Subjects with sexual dysfunction

It is important to clarify that the ensuing recommendation and accompanying comments refer to men with functional hypogonadism who complain of sexual dysfunction—as distinct from men who present with erectile or sexual dysfunction, the vast majority of whom have normal T concentrations.

### 4.1.1 | Recommendations

**Recommendation #10.** We recommend TRT in hypogonadal men with sexual/erectile dysfunction to improve libido, erectile function and sexual satisfaction (1⊕⊕⊕⊕).

### 4.1.2 | Evidence

T critically regulates sexual function, in particular libido and to a lesser extent erectile function.<sup>48,49</sup> Trials clearly documented that TRT, compared to placebo, modestly increased sexual interest and sexual activity, from flirting to sexual intercourse in hypogonadal men with  $T < 9.4$  nmol/L ( $<270$  ng/dL).<sup>6</sup> In addition, the effect size was inversely related to the baseline T concentrations and proportional to the increase in T concentrations during the study. Greater effects on libido and sexual activity than on erectile function were observed.<sup>6</sup> These data are in line with most recent meta-analyses on sexual function, which also showed that TRT is effective when T is  $<10.4$  nmol/L ( $<300$  ng/dL)<sup>50</sup> or  $12$  nmol/L ( $350$  ng/dL)<sup>18,19</sup> and ineffective in men with  $T > 12$  nmol/L ( $>350$  ng/dL).<sup>18,19</sup> In addition, a recent meta-analysis on men with functional hypogonadism suggested that TRT alone may modestly (International index of erectile function—Erectile function domain [IIEF-EFD] 2–3 points; effect size 0.30) improve mild (IIEF-EFD score 22–25), but not more severe (IIEF-EFD score  $< 22$ ) ED.<sup>19</sup> Furthermore, TRT efficacy on erectile function was higher in those with more severe hypogonadism ( $T < 8$  nmol/L or  $231$  ng/dL) and lower amongst men with T2DM and obesity.<sup>19</sup>

### 4.1.3 | Values

We place a high value on the proven efficacy of TRT in improving libido and overall sexual function in older men with functional hypogonadism. We place a lower value on the less consistent effects of TRT on erectile function in hypogonadism, especially in those with moderate or severe ED, who are prone to have concomitant underlying vascular disease.

### 4.1.4 | Remarks

The combination of TRT with phosphodiesterase-5 inhibitors (PDE5i) is often considered in hypogonadal men with more severe degrees of ED, especially if either treatment alone proved ineffective. However, available evidence is insufficient to clarify this point. A meta-analysis specifically addressing this issue did not find any benefits related to the combined use of PDE5i and TRT<sup>18</sup> although 3 out of 5<sup>51–53</sup> studies included enrolled mixed eugonadal/hypogonadal subjects. In addition, an RCT in men with ED and T concentrations  $<11.3$  nmol/L ( $<330$  ng/dL) also failed to demonstrate further improvements in erectile function with the

addition of T to an optimized regimen of sildenafil.<sup>54,55</sup> Hence, at present, the efficacy and place of combination therapy with T and PDE5i in the management of ED in functional hypogonadism remains unclear. Similarly, the efficacy of the combined use of TRT and intracavernosal injection of prostaglandin E1 (PGE-1) is unknown. Finally, limited evidence suggests that TRT may also improve delayed ejaculation in hypogonadal men.<sup>48,49,56</sup>

## 4.2 | Obesity

### 4.2.1 | Recommendations

**Recommendation #11.** We recommend against TRT as a treatment for weight reduction in obese men (1⊕⊕○○).

### 4.2.2 | Evidence

RCTs specifically designed to study the effects of TRT on weight reduction in overweight or obese men are not available. Nevertheless, TRT consistently improves body composition (similar reduction of fat mass and increase of lean mass) in hypogonadal men, without any change in total bodyweight or body mass index (BMI) when compared with placebo or diet alone.<sup>57–59</sup> Long-term effects of TRT on body composition are unknown. Data derived from registry and uncontrolled studies suggest that TRT might reduce body weight and BMI in hypogonadal men<sup>60</sup>; however, these studies have important limitations, which mitigate against their validity.

### 4.2.3 | Values

We place a high value on the recommendation that TRT alone should not be considered as an anti-obesity drug.

## 4.3 | Metabolic syndrome and/or diabetes

### 4.3.1 | Recommendations

**Recommendation #12.** We recommend against the use of TRT to improve glycometabolic control in men with type 2 diabetes (T2DM) and/or metabolic syndrome MetS (1⊕⊕○○).

### 4.3.2 | Evidence

The metabolic effects of TRT in men with T2DM and MetS are conflicting. Only few placebo-controlled RCTs specifically investigated metabolic outcomes as primary endpoint of TRT in these populations. The TIMES-2, the largest study on T2DM or MetS subjects ( $n = 220$ ), was unable to document a significant reduction in haemoglobin A<sub>1c</sub>

(HbA<sub>1c</sub>) concentrations or BMI after 26 weeks of T gel 1%, although some improvement in the homeostatic model assessment of insulin resistance (HOMA-IR) was observed.<sup>61</sup> The largest RCT conducted exclusively in 199 men with T2DM was the BLAST study.<sup>62</sup> Long-acting injectable TU for 30 weeks resulted in significant improvement of HbA<sub>1c</sub> concentrations, particularly in poorly controlled men (baseline HbA<sub>1c</sub>  $\geq$  58 mmol/mol; 7.5%). Waist circumference decreased without any modification of BMI.<sup>62</sup> In contrast, Gianatti et al<sup>63</sup> did not observe any improvement in HbA<sub>1c</sub> concentrations or HOMA-IR index in 88 men with T2DM, despite an improvement of body composition (reduction of fat mass and increase in lean mass), after 40 weeks of long-acting injectable TU when compared to placebo. Uncontrolled registry studies suggest that TU treatment may improve glycometabolic controls in men with T2DM and MetS up to 8 years<sup>64-67</sup> and prevents pre-diabetes progression to T2DM in men with hypogonadism.<sup>68</sup> The unconfirmed results of these studies have important limitations as mentioned earlier and cannot therefore be accepted as generalizable evidence. The effects of TRT on other parameters of MetS such as lipid profile and blood pressure are inconsistent.

#### 4.3.3 | Values

We place a higher value on the lack of clear evidence from RCTs that TRT consistently improves the metabolic profile (HbA<sub>1c</sub>, fasting glycaemia) or longer-term benefits in clinical outcomes in men with T2DM or MetS. We place a lower value on the inconsistent, modest short-term improvement in insulin resistance (HOMA-IR) despite the consistent effect of T on body composition. However, TRT is indicated in men with MetS or T2DM who also have diagnosed hypogonadism for the management of traditional hypogonadal symptoms without the promise (or expectation) of improvements in metabolic status.<sup>40</sup>

### 4.4 | Subjects with bone diseases

#### 4.4.1 | Recommendations

**Recommendation #13.** We recommend against TRT with the sole purpose of reducing fracture risk in hypogonadal men with high fracture risks (1 ⊕⊕⊕○).

#### 4.4.2 | Evidence

TRT may improve bone quality in hypogonadal men with low or moderate fracture risk.<sup>69</sup> TTriaLs also showed that TRT improves volumetric bone mineral density, more in the spine than (but also significantly) in the hip,<sup>6</sup> confirming earlier data that TRT increases areal spinal bone mineral density as measured by dual-energy X-ray absorptiometry (DEXA).<sup>70,71</sup> However, there are no data on the effects of TRT on fracture risk or incidence in men, unlike several bone-specific medical therapies (eg bisphosphonates).<sup>69</sup>

#### 4.4.3 | Values

In hypogonadal men with osteoporosis and/or at high risk of fragility fracture, anti-osteoporotic therapy with proven benefits on reducing fracture risk is preferred. TRT can also be prescribed at the same time in these men for the management of extant hypogonadal symptoms.

#### 4.4.4 | Remarks

Fracture risk rather than bone density is the more important outcome.<sup>69</sup> Fracture risk (estimated by FRAX or similar scores) remains the key metric for determining appropriate treatment option and assessment of efficacy in hypogonadal patients at high risk of osteoporosis.<sup>69</sup>

### 4.5 | Subjects with psychological symptoms

#### 4.5.1 | Recommendations

**Recommendation #14.** We recommend against TRT for the sole treatment to improve depressive symptoms in hypogonadal men (1 ⊕⊕○○).

#### 4.5.2 | Evidence

Few placebo-controlled RCTs have investigated the potential role of TRT for the treatment of depressive symptoms.<sup>72</sup> TRT improved mood, and depressive symptoms using several self-report instruments in the TTriaLs, although the magnitude of the effects was small.<sup>6</sup> This is in line with data reported in available meta-analyses.<sup>73-76</sup> The positive effect of TRT was confirmed only in hypogonadal patients, with apparently higher efficacy in those <60 years and those with minor depressive symptoms.<sup>74</sup>

#### 4.5.3 | Values

We place a higher value on the use of established anti-depressive therapy, cognitive behavioural therapy and psychiatric consultation in men with depressive symptoms or in those with diagnosed major depression. We place a lower value on the possibility that TRT may modestly improve mood in hypogonadal men.

#### 4.5.4 | Remarks

Information on the effects of TRT in major depressive disorders is lacking. Similarly, the outcomes on combination of TRT with established anti-depressive therapy are not available.

## 4.6 | Subjects with chronic diseases

### 4.6.1 | Recommendations

**Recommendation #15.** We recommend against the use of TRT, in the absence of symptomatic hypogonadism, to improve the morbidity and/or mortality of several chronic diseases including human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS), heart failure, obstructive pulmonary disease, chronic kidney diseases, bowel inflammatory diseases or to prevent the long-term outcomes of subjects chronically treated with glucocorticoid or opioid therapy (2 ⊕⊕○○).

### 4.6.2 | Evidence

Several chronic conditions including HIV-1 infection, particularly wasting syndrome, heart failure, chronic obstructive pulmonary disease (COPD), impaired renal function, in particular end-stage renal diseases (ESRD) as well as bowel inflammatory diseases, are frequently associated with lower T concentrations.<sup>77,78</sup> Limited evidence suggests that TRT might improve lean mass in HIV<sup>77,79,80</sup> and in COPD<sup>81</sup> patients. No data, however, indicate that TRT may impact on either natural course or long-term outcomes of chronic diseases. This also applies to men with chronic inflammatory diseases treated with glucocorticoids.<sup>77</sup>

### 4.6.3 | Values

We place a higher value on recommending against the use of TRT with the intention of modifying the natural course of chronic diseases, and a lower value on improving hypogonadal (mainly sexual) symptoms in patients with chronic diseases and low T, due to the lack of supportive evidence on overall clinical benefits and improvements in quality of life.

## 4.7 | Ageing men

### 4.7.1 | Recommendations

**Recommendation #16.** We recommend against routinely prescribing T to men >65 years as an anti-ageing therapy (1 ⊕⊕⊕⊕).

**Recommendation #17.** We recommend against TRT in frail men to improve exercise capacity/physical function (1 ⊕⊕⊕⊕).

**Recommendation #18.** We recommend against TRT in ageing men to improve cognitive function (1 ⊕⊕⊕⊕).

### 4.7.2 | Evidence

The role of TRT in elderly men remains a matter of considerable debate. The TTrialS showed that TRT did not substantially

increase walking distance in the cohort of men complaining of low physical function.<sup>6</sup> However, walking distance increased significantly when the whole study population was included in a sub-analysis. In line with these findings, the post hoc analysis of the data showed that TRT consistently improved self-reported walking ability as well as modestly improved 6 minutes walk test (across all TTrial participants), but did not affect falls.<sup>83</sup> In addition, although TRT did not improve vitality as assessed by an increase above the pre-specified threshold value in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale as the primary outcome, it did improve vitality, mood and depressive symptoms as continuous measures by several instruments.<sup>6</sup> The magnitude of each of these improvements, however, was small and their clinical significance uncertain. Finally, TRT did not improve cognitive performance.<sup>6</sup>

### 4.7.3 | Values

We place a higher value on the view that the TRT has not been shown unequivocally to improve physical, cognitive function or energy level, in elderly men with low T concentrations, to an extent that is likely to provide patient-important benefits. We place a relatively lower value on the results of the TTrialS, which show modest improvements in these functional domains. Our opinion is influenced by the current lack of data on long-term safety of TRT in elderly men (see below).

## 5 | SAFETY AND CONTRAINDICATIONS

Safety data on cardiovascular diseases (CVD), VTE and prostate cancer risks pertain only to short-term treatment, since the vast majority of RCTs on TRT exposed subjects to T for 6-24 months, with the maximum duration of 36 months.<sup>7</sup> Furthermore, none of the studies has been sufficiently powered to exclude adverse event risks in the longer term.

### 5.1 | Prostate and breast

#### 5.1.1 | Recommendations

**Recommendation #19.** We recommend against TRT in men with untreated prostate or breast cancer (Good Clinical Practice statement).

**Recommendation #20.** We recommend, before initiation of TRT in men > 40 years of age, discussing potential benefits and risks of prostate cancer screening and engaging the patient in shared decision-making regarding options for pre-treatment screening and on-treatment monitoring (see *Recommendations #21, #22, #31, #32*). These discussions should also take into account local guidelines for prostate cancer screening for the general population (Good Clinical Practice statement).

**Recommendation #21.** We recommend, before initiating TRT in men > 40 years of age, checking prostatic-specific antigen (PSA) and performing digital rectal examination (DRE) of the prostate to minimize the risk of prescribing T to patients with undiagnosed prostate cancer (1⊕⊕○○).

**Recommendation #22.** We recommend against TRT in men with PSA > 4 ng/mL (or elevated PSA according to local/national guidelines) or prostate abnormalities on DRE without further evaluation and/or urological consultation (1⊕⊕○○).

**Recommendation #23.** We suggest TRT should not be used in men with severe lower urinary tract symptoms (LUTS) [International Prostate Symptom Score (IPSS)>19] (2⊕○○○).

### 5.1.2 | Evidence

Androgens and/or oestrogens are known to stimulate proliferation and differentiation of prostate<sup>84,85</sup> and breast cancers.<sup>86</sup>

However, increased short-term (mostly < 12 months, maximum three years) risk of incident prostate cancer, prostate-related adverse events, increase in LUTS or prostate volume or breast cancer have not been documented following TRT in men with low T.<sup>85,86</sup> TRT in men with treated prostate cancer remains controversial, with only scarce evidence to support its safety.<sup>84,85,87</sup> Information on the use of TRT in men with breast cancer following curative treatment is not available.<sup>86</sup>

Low, rather than high T seems to be associated with benign prostatic hyperplasia (BPH) and LUTS.<sup>88</sup> A recent meta-analysis did not show an increase of LUTS severity in hypogonadal men treated with T vs placebo.<sup>89</sup> Limited information, however, is available in men with severe LUTS (ie IPSS score > 19) as well as in those with PSA concentrations > 4 ng/mL<sup>88,89</sup> since they are usually excluded from enrolment into TRT trials.

### 5.1.3 | Values

We place a high value on the current lack of long-term prostate safety data on TRT in men with functional hypogonadism. TRT is contraindicated in hypogonadal men with untreated prostate and breast cancer in accordance with good clinical practice. In view of the conflicting evidence and continuing controversies,<sup>90</sup> patients should be counselled about the potential benefits and risks of prostate cancer screening and be involved in shared decision-making regarding options for pre-treatment screening. When available, local guidelines for prostate cancer screening for the general population should also be considered.

### 5.1.4 | Remarks

PSA represents a continuous parameter directly related to the likelihood of prostate cancer, although an optimal PSA threshold for

detecting non-palpable but clinically significant prostate cancer has not been completely identified.<sup>90</sup> An elevated PSA level of >4 ng/mL (or elevated PSA according to local/national guidelines) should be confirmed a few weeks later under standardized conditions (ie no ejaculation, prostate manipulations, and urinary tract infections) in the same laboratory. Elevated PSA concentrations, if confirmed, require further evaluation.<sup>90</sup>

In severely symptomatic hypogonadal men with treated (radical prostatectomy) low-grade prostate cancer (Gleason score < 7) who remained in remission (with undetectable PSA for at least two years), the possible risks and benefits of TRT should be discussed with the patient and his oncologist and/or urologist in order to reach an individually appropriate joint decision on management.<sup>91</sup> The safety of TRT in men with severe LUTS remains to be established but modest LUTS (IPSS ≤ 19) is not a contraindication to TRT.<sup>88,89</sup>

## 5.2 | CVD and venous thromboembolism risks

### 5.2.1 | Recommendations

**Recommendation #24.** We recommend against TRT in men with severe heart failure [New York Heart Association (NYHA) Class III or IV] (1⊕⊕○○).

**Recommendation #25.** We suggest against TRT in patients with a recent major acute CV event (including stroke) (2⊕⊕○○).

**Recommendation #26.** We suggest against TRT in men with documented polycythaemia and/or elevated haematocrit (>48%-50%) depending on associated morbidities and CV risk without further evaluation (2⊕⊕○○).

**Recommendation #27.** We suggest obtaining detailed personal and family history of venous thromboembolism (VTE) and risk factors for VTE prior to initiating TRT (2⊕○○○).

### 5.2.2 | Evidence

The risks of TRT in patients with class III or IV heart failure have not been formally documented. These patients often represent a frail immobile population, at risk of polycythaemia and VTE, which are further contraindications for TRT (see below).

The association between CVD and TRT was highlighted by the US Food and Drug Administration (FDA), which instigated a label warning on all T products. Similar conclusions were reached by Health Canada. Conversely, the European Medicine Agency (EMA) did not find sufficient evidence for declaring a TRT-associated CV risks (see for review Ref. [2]). A recent meta-analysis including 15 pharmaco-epidemiological and 93 RCTs showed no clear evidence of increased CV risk related to TRT<sup>92</sup> but none of these studies was designed (with sufficiently long duration of exposure) or powered (with sufficient numbers of participants) to exclude such a risk. At the behest of the US FDA, an industry-supported multi-centre RCT is underway to investigate the CV risk of TRT (clinicaltrials.gov: NCT03518034).

High haematocrit (Hct) is a risk marker of CV morbidity, mortality and VTE.<sup>93</sup> In a 28-year follow-up study amongst 670 men aged 55 years, Hct > 50% was associated with 1.8-fold increase in coronary heart disease (CHD) mortality even after adjustment for established coronary risk factors.<sup>94</sup> The Framingham Heart Study reported that in men older than 64 years of age, Hct > 48% was associated with higher CHD and CVD mortality.<sup>95</sup> Since no clear Hct threshold was associated with an increased CV risk, the final decision to start or not TRT should be left to the physician considering overall patient clinical conditions. Several associated morbidities including COPD, obstructive sleep apnoea syndrome, heart failure (HF) as well as smoking habit can potentially further contribute to TRT-associated increment of Hct. Hence, Hct > 48%-50%, depending on associated morbidities and CV risk, can be considered a contraindication for initiating TRT without further investigation. Several case series also documented VTE in patients who received TRT, and both the US FDA<sup>96</sup> and Health Canada<sup>97</sup> warned against the risk of VTE in all T products, requiring a label change. Conversely, two large population-based studies failed to find an association between endogenous T and VTE (<sup>98,99</sup>; see Ref. [100] for review). However, a more recent Mendelian randomization study from the UK Biobank, including around 500 000 men aged 40-69, showed that endogenous T, genetically predicted by variants in the JMJD1C gene region, was positively associated with thromboembolism.<sup>101</sup> It is also important to recognize that the vast majority of the previously reported cases of TRT-related VTE may have been related to undiagnosed thrombophilia-hypofibrinolysis, emphasizing the role of past and family history of thromboembolic diseases.<sup>100,102</sup>

### 5.2.3 | Values

We place a high value on the current lack of definitive long-term CVD risk data on TRT in men with functional hypogonadism, while acknowledging the safety warnings from North America.<sup>103</sup> However, our preference is to follow the guidance from the EMA stating that when hypogonadism is properly diagnosed and managed, there is currently no consistent evidence of an increased risk of CV disease during TRT.<sup>104</sup>

### 5.2.4 | Remarks

It should be important to recognize that the proposed criteria related to Hct thresholds are derived from the general population not living at high altitudes.

## 5.3 | Fertility

### 5.3.1 | Recommendations

**Recommendation #28.** We recommend against TRT in hypogonadal men who desire fertility (1⊕⊕⊕⊕).

### 5.3.2 | Evidence

TRT suppresses gonadotrophins and endogenous T secretion as well as spermatogenesis. Data derived from the use of anabolic steroids indicated that such suppression may even persist many months (up to 12 months usually but sometimes more) after treatment discontinuation.<sup>105</sup>

### 5.3.3 | Values

TRT is contraindicated in men with function hypogonadism who desire fertility<sup>106</sup> (see Section 7.8).

## 6 | MONITORING

The follow-up of T treatment in patients with functional hypogonadism, in general, should be no different from organic hypogonadism. The EAA guidelines, therefore, largely agrees with the recent US and Australian Endocrine Society guidelines.<sup>5,20</sup>

### 6.1 | Monitoring TRT for functional hypogonadism

#### 6.1.1 | Recommendations

**Recommendation #29.** We recommend assessing the clinical response as well as adverse effects to TRT at 3 and 12 months after initiation of treatment. Thereafter, clinical review should be scheduled at least yearly (1⊕⊕⊕⊕).

**Recommendation #30.** We suggest that on-treatment total T concentrations should be measured at each clinic visit to ensure that average total T concentrations achieve the targeted mid-normal range for young men (2⊕⊕○○).

**Recommendation #31.** We suggest performing digital rectal examination and checking PSA at 3 to 12 months for men > 40 years of age after initiating T treatment. After the first 12 months, local guidelines for prostate cancer screening for the general population should be followed (2⊕○○○).

**Recommendation #32.** We suggest further evaluation and/or urological consultation, if there is: (a) an increase in serum PSA concentration >1.4 ng/mL within 12 months of initiating T treatment, (b) a confirmed PSA > 4 ng/mL at any time and (c) detection of a prostatic abnormality on DRE or a substantial worsening of LUTS (2⊕○○○).

**Recommendation #33.** We recommend measuring the haematocrit (Hct) 3-6 months after initiation of TRT and then annually. If Hct is >54%, TRT should be discontinued, until Hct decreases to a safe level; evaluate the patient for hypoxia and sleep apnoea; reinstate therapy with a reduced dose (1⊕⊕⊕⊕).



### 6.1.2 | Evidence

At each clinic review, serum T concentration should be checked to ensure that the normal range for young men 9.6-30 nmol/L (280-873 ng/dL)<sup>6</sup> is attained (Figure 1; see Recommendation #29, above). There is a general consensus that Hct > 54% requires TRT withdrawal (and sometimes phlebotomy) to minimize the risks of VTE and CV events.<sup>93</sup>

### 6.1.3 | Values

We place a high value on minimizing the risk of unnecessary prostate biopsy (resulting in over-diagnosis of clinical inconsequential prostate cancer in situ or high-grade prostatic intraepithelial neoplasia, infection, cost, etc) as a consequence of prostate safety monitoring.

In view of the conflicting evidence and continuing controversies,<sup>90</sup> patients should be counselled about the potential benefits and risks of prostate cancer screening for on-treatment monitoring. These discussions should also take account of local guidelines (when available) for prostate cancer screening for the general population. In line with the European Association of Urology (EAU) guidelines,<sup>90</sup> in men >40 years, who have initiated TRT, we suggest (after discussing potential benefits and risks of prostate screening) engaging the patient in shared decision-making regarding continued monitoring after the first 12 months of treatment. In men >40 years at increased risk of prostate cancer (eg men of African descent and those with a first-degree relative with diagnosed prostate cancer or previously positive prostate biopsy, and in those with baseline PSA concentrations >1 ng/mL at age 40 years or >2 ng/mL at age 60 years), having initiated TRT, we suggest (after discussing prostate cancer risk with the patient) offering continued monitoring options after the first 12 months of treatment. The risk of prostate cancer in men younger of 40 years is very low, whereas the risk of dying from prostate cancer (as opposed to other co-morbidities) in men diagnosed when they are 70 years of age or older has been not considered high enough to warrant monitoring in the general population.<sup>90</sup> The use of cancer risk calculators<sup>107</sup> can allow clinicians to identify patients at higher risk for prostate cancer.<sup>90</sup>







### 6.1.4 | Remarks

The exact timing for T evaluation depends on the T preparation used.<sup>5</sup> Dose adjustment, switching to alternate T preparations or (dis)continuation of treatment can be guided by the clinical response and the on-treatment T concentration. It is important to be reminded that many cases of functional hypogonadism are potentially reversible. Thus, TRT withdrawal may be considered following weight reduction or if medications such as opiates can be stopped or substituted. If TRT does not result in significant clinical improvement after 6 months, treatment should be discontinued, and alternate diagnosis sought. Temporary treatment 'holidays' will allow the HPT axis function to be reassessed and the requirement for continuation of TRT determined.

## 7 | CONCLUSIONS

Functional hypogonadism is a relatively new clinical diagnosis that is still not universally recognized or accepted. T concentrations decline gradually with age, but the clinical significance of low T in ageing men remains unclear. This presents a difficult challenge to clinicians who are charged with confirming a genuine diagnosis of (functional) hypogonadism amongst a plethora of relatively non-specific symptoms (of which sexual symptoms show the strongest association with T deficiency). This is compounded by the fact that T concentrations in functional hypogonadism are commonly found in the borderline (8-12 nmol/L) rather than the unequivocally pathological range (<6 nmol/L). In this situation, fT measurement can be helpful in resolving borderline cases. It is important to recognize the roles of obesity and co-morbidity as well as medications in aggravating the natural age-related T decline, with the important implication of potential reversibility. Thus, TRT, more often than not, initiated as a therapeutic trial, should not be continued if there is no clinical improvement. Moreover, the diagnosis and changing requirements/priorities of the patient should be reviewed regularly, especially of those in advanced age whose risk and benefit balance may shift with time. The present recommendations for or against treatment are substantially influenced by the fact that real clinical benefits and safety (especially in the longer term) of TRT have not been fully documented. Furthermore, due to its potential reversibility, no data are currently available to recommend the appropriate duration of TRT in individual patients with functional hypogonadism. It is clear that this is an evolving area of clinical practice that requires much more clinical research efforts. The relative abundance of negative rather than positive recommendations (which may not always be definitive) in these guidelines reflects a dearth of high-level evidence. In the meantime, clinicians dealing with individual patients with possible functional hypogonadism should be prepared to explicitly discuss the uncertainties of the potential risks and benefits of TRT from current evidence and engage them in shared management decision-making.

### ORCID

Giovanni Corona  <https://orcid.org/0000-0002-9894-2885>  
 Dimitrios G. Goulis  <https://orcid.org/0000-0002-5005-1995>  
 Ilpo Huhtaniemi  <https://orcid.org/0000-0001-9092-7886>  
 Michael Zitzmann  <https://orcid.org/0000-0003-3629-7160>  
 Jorma Toppari  <https://orcid.org/0000-0003-2228-334X>  
 Dirk Vanderschueren  <https://orcid.org/0000-0003-1395-0104>  
 Frederick C. Wu  <https://orcid.org/0000-0002-7005-4798>

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## APPENDIX

The manuscript has been approved by the European Academy of Andrology (EAA) Guidelines Committee members (G. Corona, D.G. Goulis, G. Forti, H.M. Behre, M. Punab, J. Toppari, C. Krausz), EAA Executive Council (C. Krausz, Ewa Rajpert-De Meyts, Frank Tüttelmann, A.M. Isidori, Eduard Ruiz-Castane, Davor Jezek, Zsolt Kopa, J. Toppari, M. Simoni), EAA Center Directors and the Co-Editor-in-chief (M. Simoni).

In addition, the manuscript has been revised and approved by Andrea Isidori and Mario Maggi on behalf of the European Society of Endocrinology.