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Consensus Recommendations

Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions

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Abstract

To address widespread concerns regarding the medical condition of testosterone (T) deficiency (TD) (male hypogonadism) and its treatment with T therapy, an international expert consensus conference was convened in Prague, Czech Republic, on October 1, 2015. Experts included a broad range of medical specialties including urology, endocrinology, diabetology, internal medicine, and basic science research. A representative from the European Medicines Agency participated in a nonvoting capacity. Nine resolutions were debated, with unanimous approval: (1) TD is a well-established, clinically significant medical condition that negatively affects male sexuality, reproduction, general health, and quality of life; (2) symptoms and signs of TD occur as a result of low levels of T and may benefit from treatment regardless of whether there is an identified underlying etiology; (3) TD is a global public health concern; (4) T therapy for men with TD is effective, rational, and evidence based; (5) there is no T concentration threshold that reliably distinguishes those who will respond to treatment from those who will not; (6) there is no scientific basis for any age-specific recommendations against the use of T therapy in men; (7) the evidence does not support increased risks of cardiovascular events with T therapy; (8) the evidence does not support increased risk of prostate cancer with T therapy; and (9) the evidence supports a major research initiative to explore possible benefits of T therapy for cardiometabolic disease, including diabetes. These resolutions may be considered points of agreement by a broad range of experts based on the best available scientific evidence.

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On October 1, 2015, an international expert consensus conference regarding testosterone (T) deficiency (TD) and its treatment was held in Prague, Czech Republic. The meeting was sponsored by King's College London and the International Society for the Study of the Aging Male. The impetus for holding this meeting was to address the considerable degree of misinformation and confusion regarding this topic that has arisen in the medical and lay press over the past several years, due in great part to intense media attention on 2 reports suggesting increased cardiovascular (CV) risk.[1,2] The circumstances of this meeting, but not the proceedings, have been described previously.[3]

Participants were invited on the basis of their clinical and/or research expertise with TD and represented a broad range of specialties from 11 countries on 4 continents. The objectives of the meeting were to address key issues in the field of T therapy to determine if consensus could be reached by a broad range of experts on the basis of the highest-quality available evidence. This article presents the 9 statements, termed *resolutions*, discussed by participants and agreed upon by consensus. All 9 resolutions received unanimous approval.

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Unlike standard guidelines that provide practical clinical recommendations regarding the evaluation and management of TD, our focus was to address fundamental concepts within the field that have been questioned and challenged. We concentrated on the scientific evidence in order to address concepts and related questions that have arisen in the scientific and lay media. The ultimate goal is to provide a document that establishes what is true, or untrue, to the best degree possible based on existing scientific and clinical evidence. Importantly, this conference addressed only the medical condition of TD and the medically indicated use of T therapy. We specifically did not discuss the use of androgens for athletic performance enhancement, bodybuilding, or any other non—medically indicated use.

Recognition of the historical context that led to this meeting is important. Testosterone therapy has been available for clinical use since at least the 1940s, but until the past 20 years, its use was restricted almost exclusively to men with the most severe cases of TD, such as men with pituitary tumors or anorchia.[4] More frequent use of T therapy began in the 1990s when clinical experience and research determined that otherwise healthy men could have symptoms related to TD that often responded to T therapy, and further increases in use accompanied the introduction of more convenient formulations in the early 2000s.

Testosterone use has long been controversial, even before the recent increase in prescriptions for T products, associated with illicit athletic performance enhancement and bodybuilding as an anabolic steroid.[5] Medically, the greatest concern for 7 decades had been the fear of precipitating aggressive prostate cancer (PCa).[6] However, negative media stories peaked with publication of a retrospective study reporting increased CV risks in a leading medical journal in November 2013.[1] Two months later, in January 2014, a second retrospective data analysis reported increased nonfatal myocardial infarction (MI) rates following a T prescription compared with the rate before the prescription.[2] Two days later, the US Food and Drug Administration (FDA) announced it would investigate CV risk with T products.

Numerous articles and opinion pieces in the media commented on the dangers of T therapy on the basis of these reports.[7] Many included comments from physicians that contained erroneous or distorted information regarding the indications, benefits, or risks regarding T therapy. Health Canada and the FDA subsequently added warnings regarding CV risk to T products. The FDA added additional restrictions on the use of T therapy, limiting its indication to men with identified underlying etiologies for TD and rejecting the concept of "age-related hypogonadism."[8] In contrast, the European Medicines Agency (EMA) declined to add a warning based on its review of the evidence.[9]

The intense media attention to this issue has impacted the clinical care of men with TD. In the United States, clinicians have noted that patients with long histories of benefits from T therapy discontinued treatment because of fear that they would experience a CV event. In Singapore, the Ministry of Health sent a bulletin to physicians dated March 4, 2015, that identified a number of practices, including "testosterone for hormonal replacement," as being "not evidence based," with threats of sanctions for its continued use. A subsequent revision allowed for treatment when there was laboratory confirmation of TD, but these directives added to physician confusion.[10]

As with any field, there are many areas of controversy within the field of TD and its treatment. However, our objective in convening this conference was to establish a basic set of concepts that could be agreed upon by a broad base of experts within the field and that such agreement would represent the *absence* of major controversy on those topics by experts familiar with the entire range of literature on the topic and informed further by clinical experience with TD and T therapy. This article presents 9 resolutions that address fundamental concepts, including several that are often described as controversial but registered uniform approval among our expert participants. We hope that this document will provide a solid scientific foundation for further discussions for scientists, clinicians, and our patients.

TERMINOLOGY

It was agreed that we would use the following terminology, consistent with an effort to use language that promotes accuracy and clarity: *testosterone therapy* (*T therapy*) rather than the older term *testosterone replacement therapy*; and *testosterone deficiency* (*TD*) rather than the

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older term *hypogonadism*. We note that the term *low T* is an informal, non-technical term for TD, analogous to the use of "heart attack" in place of MI.

PARTICIPANTS

Broad geographic and specialty distribution of the expert panel was achieved. There were 18 participants from 11 countries on 4 continents. Specialties included urology, endocrinology, internal medicine, diabetology, and basic science research. Experts were invited on the basis of extensive clinical experience with TD and its treatment, research experience, or both. Our goal in achieving such broad geographic and specialty representation was to provide assurance that resolutions that met broad approval were likely to reflect the opinions of a wide base of experts from around the world and to minimize regional- or specialty-based biases and groupthink. Because of the involvement of regulatory agencies in the public debates regarding T, invitations to participate were extended to the FDA and to the EMA; a representative from the EMA did attend in a nonvoting capacity. King's College London provided the services of Dr Anthony W. Fox, who served as meeting secretary. All experts volunteered their time, and the authors of this article received no honoraria for services rendered.

METHODS

A set of 9 statements, termed *resolutions*, were prepared by a working group and circulated to the participants before the conference. At the conference, the relevant science and literature were presented by one expert (presenter), followed by comments by a second expert (discussant). The resolution then underwent vigorous discussion by the entire consensus panel, including debate regarding final wording of the resolution. As a consensus conference, there was no requirement for unanimity: however, all resolutions passed with unanimous support. Several resolutions were modified as a result of the discussion before approval by the group.

The body of the final document, presented in this article, consists of short abstracts of the science behind each resolution, prepared initially by the presenter of that topic at the conference with revisions by the discussant. These sections were then edited to produce a consistent length and style, and the final document was then reviewed and approved by all voting participants. In addition to the major statements encompassed by the 9 resolutions, a set of up to 5 additional related points were added at the time of the conference and refined further for the final document (Table 1). Together with the resolutions themselves, these points may be regarded as take-home messages for the public, clinicians, and scientists.

In order to provide a readable, accessible document, we chose to limit the length of each section and supporting references to approximately 250 to 350 words and up to 10 references. No attempt was made to provide a comprehensive review of any topic. Instead, key points, perspectives, and references are included in this article. The 9 resolutions and additional key points are summarized in Table 1.

The choice of topics presented in this article was made with the goal of finding common ground among experts in order to provide a solid foundation for further discussions. These topics were considered to be noncontroversial to experts, even though they may appear controversial to nonexperts on the basis of media reports. The fact that there was unanimous support for each of the resolutions should not be interpreted to imply that there is universal agreement on these points by all experts, nor that there are no other areas of serious debate. However, the unanimous support for each of the resolutions discussed subsequently should provide comfort that there is broad agreement on these key points among experienced scientists and clinicians in this field.

RESOLUTION 1. TD IS A WELL-ESTABLISHED, SIGNIFICANT MEDICAL CONDITION THAT NEGATIVELY AFFECTS MALE SEXUALITY, REPRODUCTION, GENERAL HEALTH, AND QUALITY OF LIFE

Testosterone has a broad range of physiologic functions affecting multiple organ systems, including the brain, peripheral nerves, muscle, fat, bone, CV system, and male genital and reproductive systems. It regulates the metabolism of carbohydrates, lipids, and proteins and influences muscle growth and adipogenesis. Recognized as an important medical condition since at least 1940,[4] TD is a well-established, major medical condition that negatively impacts male sexuality, reproduction, general health,

TABLE 1. Resolutions of the International Expert Consensus Conference on Testosterone Deficiency and Its Treatment

Resolutions	Expert comments
1. TD is a well-established, significant medical condition that negatively affects male sexuality, reproduction, general health, and quality of life	○ TD (low levels of testosterone) • May predict increased risk of developing diabetes, metabolic syndrome • Contributes to decreased bone mineral density • Is associated with increased all-cause and cardiovascular mortality • Negatively impacts general health and quality of life
2. The symptoms and signs of TD occur as a result of low levels of T and may benefit from treatment regardless of whether there is an identified underlying etiology	• Symptoms and signs of TD occur in healthy volunteers or patients who undergo androgen deprivation; these symptoms and signs resolve with T normalization • Historically recognized causes of TD are rare (eg, anorchia, craniopharyngioma, pituitary tumor), recently termed *classical hypogonadism.* These conditions account for only a tiny fraction of men with TD • TD occurs frequently with conditions other than "classical" causes • No evidence exists to support restriction of T therapy only to men with known underlying etiology
3. TD is a global public health concern	• Prevalence rates in men range from 2% to 38% in studies from Asia, Europe, North America, and South America • Variation in prevalence rates can be explained by differences in the operative definition of TD and biochemical thresholds • A US study estimates an additional $190-$525 billion in health care expenditures over 20 years due to TD
4. T therapy for men with TD is effective, rational, and evidence based	○ High-level evidence shows T therapy effectively: • Increases sexual desire (libido) and erectile and orgasmic function • Increases lean body mass • Decreases fat mass • Improves bone mineral density ○ Strongly suggestive evidence for improvement in mood, energy
5. There is no T concentration threshold that reliably distinguishes those who will respond to treatment from those who will not	No study has revealed a single testosterone threshold that reliably separates those who experience signs and symptoms of TD from those who do not, nor who will likely respond to treatment. Interpretation of total T concentrations is confounded by: • Interindividual variation • Variation in serum SHBG (binds tightly to T, removing it from the bioavailable pool) • Genetic variation in androgen sensitivity due to *AR* gene polymorphisms (number of CAG repeats) Free T can be a useful indicator of androgen status
6. There is no scientific basis for any age-specific recommendations against the use of T therapy in men	• The term *age-related hypogonadism* is of questionable validity since the decline in mean serum T level with age is minor and primarily attributable to comorbidities, especially obesity • Older men respond well to T therapy, as do younger men • Increased risk of erythrocytosis in older men requires monitoring but does not merit withholding T therapy if indicated • It is illogical to single out TD as the one medical condition among many (eg, diabetes, hypertension, heart disease, cancer, arthritis) that does not merit treatment because it becomes more prevalent with age

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TABLE 1. Continued

Resolutions	Expert comments
7. The evidence does not support increased risks of CV events with T therapy	• Two observational studies received intense media attention after reporting increased CV risks. Both had major flaws/limitations. One misreported results, the other had no control group • Low serum T is associated with increased atherosclerosis, coronary artery disease, obesity, diabetes, and mortality • Several RCTs in men with known heart disease (angina, heart failure) showed greater benefits with T vs placebo (greater time to ischemia, greater exercise capacity) • The largest meta-analysis showed no increased risk with T therapy; *reduced* risk was noted in men with metabolic conditions • No increased risk of venothrombotic events with T therapy
8. The evidence does not support increased risk of PCa with T therapy	• Serum androgen concentrations are not associated with increased risk of PCa nor aggressive disease • T therapy has no greater risk of PCa than placebo • Aggressive/high-grade PCa is associated with *low* serum T levels • Early data suggest no increased risk of recurrence/progression with T therapy in men previously treated for PCa
9. The evidence supports a major research initiative to explore possible benefits of T therapy for cardiometabolic disease, including diabetes	• A large body of evidence suggests lower serum T concentrations are associated with increased CV risk; higher levels are protective • T therapy reliably increases lean mass, decreases fat mass, and may improve glycemic control • Mortality rates are reduced by half in men with TD who received T therapy compared with untreated men in observational studies • Among men who received T therapy, those with normalized T levels had a reduced rate of CV events/mortality vs men with persistently low T

CAG = cytosine, adenine, guanine; CV = cardiovascular; PCa = prostate cancer; RCT = randomized controlled trial; SHBG = sex hormone–binding globulin; T = testosterone; TD = testosterone deficiency.

and quality of life. Testosterone deficiency negatively impacts male physical function by reducing muscle mass and strength and negatively impacts sexual function by reducing libido, increasing erectile and orgasmic dysfunction, and compromising overall sexual activity.[11] It may cause impaired male fertility in some individuals. Testosterone deficiency has been reported to be associated with insulin resistance, inflammation, dyslipidemia, metabolic syndrome, and vascular risk.[12-14] It contributes to adiposity, bone loss, and anemia. Symptoms may also include depressed mood, reduced motivation, fatigue, and decreased quality of life.[15] A substantial body of evidence indicates that coronary artery disease incidence and severity, carotid intima-media thickness, atherosclerosis, and mortality are inversely correlated with serum T concentrations.[16] There is a need for greater awareness among the medical community of the impact of TD on general health and particularly on CV risk.

RESOLUTION 2. THE SYMPTOMS AND SIGNS OF TD OCCUR AS A RESULT OF LOW LEVELS OF T AND MAY BENEFIT FROM TREATMENT REGARDLESS OF WHETHER THERE IS AN IDENTIFIED UNDERLYING ETIOLOGY

The clinical manifestations of TD arise as a direct result of low circulating androgen concentrations. Diminished T concentrations may occur in the presence of known underlying conditions or in association with comorbidities such as diabetes and obesity, or the cause may be unknown. A state indistinguishable from TD can be reproduced in healthy volunteers by pharmacologically lowering serum T levels and in men with advanced PCa who undergo androgen deprivation.

Resolution of signs and symptoms consistent with TD occurs with restoration of normal testosterone concentrations.

In general, testosterone deficiency has been conceptualized as being due to a defect in the hypothalamic-pituitary-gonadal axis. Hypothalamic disease from hypogonadotropic hypogonadism can be caused by a craniopharyngioma or by Kallmann syndrome. Pituitary tumors, granulomatous invasion of the pituitary gland, or prolactinomas can cause centrally mediated hypogonadism. Primary testicular failure can result from mumps orchitis, Klinefelter syndrome, chemotherapy, or radiation. These long-recognized causes of TD have recently been termed *classical hypogonadism*.[8] Interestingly, the underlying pathophysiology of many of these textbook causes of TD took decades to fully understand.

More recently, additional causes or associations with TD have been recognized, including obesity, diabetes, the metabolic syndrome, infection with the human immunodeficiency virus, chronic renal failure, and certain medications, including long-term glucocorticoid and opioid use.[17,18] It is likely that additional causes will be identified in the future.

The clinical response to T therapy appears unrelated to underlying etiology. Indeed, all modern T trials are comprised of large majorities of men without classical hypogonadism because those historically recognized conditions are rare.[19] The recently published Testosterone Trials, the largest randomized controlled trial (RCT) to date, found considerable benefits of T therapy in a population of men without classical hypogonadism.[20] Thus, there appears to be no scientific basis to recommend restricting T therapy only to men with an identified underlying etiology, although there is value in attempting to identify such conditions when possible. Our knowledge regarding the pathophysiology of TD is incomplete, and we anticipate expanding our knowledge with further research. It is a matter of clinical judgment whether to first attempt to correct underlying comorbidities, such as obesity, or to offer T therapy immediately.[18,21]

RESOLUTION 3. TD IS A GLOBAL PUBLIC HEALTH CONCERN

Epidemiological data suggest that TD is common worldwide, albeit with widely varying reported frequencies among studies and countries.[22] This variability is attributable to the studied populations, instruments used to identify TD/hypogonadism, and differences in applied biochemical thresholds for T. In the United States, 4 studies reported prevalence rates ranging from 6% to 30%.[23-26] The European Male Ageing Study reported an overall prevalence of TD of 2.1% in men based on the presence of 3 identified sexual symptoms together with a total T level of less than 11 nmol/L (approximately 320 ng/dL) and a low free T concentration.[11] Reported prevalence rates in several Asian countries include 26% in Singapore, 20% in Japan, 19% in Malaysia, 30% in China, 26% in India, 9.5% in Hong Kong, 28% in South Korea, and 19% to 30% in Taiwan. Reported prevalence rates in men with obesity, diabetes, or the metabolic syndrome from Australia and South America range from 14% to 43%.[22] These values are consistent with the results of studies from other parts of the world, underscoring the high prevalence of TD among men with metabolic conditions.

The impact of TD affects men symptomatically but also has been found to predict the development of diabetes, metabolic syndrome, and osteoporosis, conditions with serious implications for public health. One US study estimated that over a 20-year period, TD would be directly responsible for approximately $190 to $525 billion in inflation-adjusted US health care expenditures, particularly in regard to its effect on obesity.[27] On a global scale, this amounts to an enormous public health and financial burden. In a US study, only 12% of T-deficient men, defined by the combination of symptoms and T concentrations of less than 300 ng/dL (10.4 nmol/L) received T therapy despite adequate access to medical care.[28] This percentage of treated men is likely much lower in other parts of the world. Given the noted benefits of T therapy, not only for symptoms but also for general health and metabolic conditions, there is an urgent need to study the potential positive impact of T therapy on public health costs and outcomes.

RESOLUTION 4. T THERAPY FOR MEN WITH TD IS EFFECTIVE, RATIONAL, AND EVIDENCE BASED

Population studies suggest that sexual symptoms are the most consistent symptoms

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associated with TD.[11] A recent meta-analysis of available RCTs (29 studies, 1930 patients) indicates that T therapy significantly improves erectile function, sexual-related erections, and sexual desire.[29] Of importance, these improvements were observed in men with TD but not in eugonadal or mixed populations. Orgasmic function was improved as well. The severity of TD at baseline was positively associated with a positive response to T therapy. The Testosterone Trials confirmed significant benefits of T therapy vs placebo for erections, libido, and sexual activity.[20] This large RCT also found significant improvement in mood with T therapy.[20]

In a separate meta-analysis (59 RCTs, 5078 patients), T therapy was found to significantly reduce fat mass and increase muscle mass.[30] No significant effect on weight, waist circumference, and body mass index (BMI) was noted in these RCTs, which differs from results from observational studies in which reduced weight, waist circumference, and BMI have been reported.[31,32] This difference may be due to a shorter duration of observation in RCTs. A positive effect has also been reported for T therapy on fasting glucose concentrations and homeostatic model assessment (HOMA index), with no significant changes in lipid metabolism or blood pressure.[29] In multivariate analysis, positive effects on glucose metabolism were related to the increase in lean mass.[29] In the limited number of RCTs that evaluated the combination of lifestyle modifications (diet and/or exercise) with T therapy (5 studies, 243 patients), the latter was found to provide additional benefits to lifestyle modifications alone.[33] A positive effect of T therapy on lumbar bone density is suggested by the few RCTs that investigated this issue.[34] In conclusion, T therapy for men with TD is effective, rational, and evidence based for issues related to sexual function and body composition. Further study is required to provide definite conclusions regarding the benefits of T therapy for other signs and symptoms of TD.

RESOLUTION 5. THERE IS NO T CONCENTRATION THRESHOLD THAT RELIABLY DISTINGUISHES THOSE WHO WILL RESPOND TO TREATMENT FROM THOSE WHO WILL NOT

There is no clear-cut T threshold that reliably distinguishes men who will respond to treatment from those who will not, a fact acknowledged by the Endocrine Society in the United States, among others.[35] Rather, TD symptoms and signs become more likely with decreasing T levels. Testosterone-related loss of libido or vigor increases below T concentrations of 15 nmol/L, increased visceral fat is observed below concentrations of 12 nmol/L, and depression and type 2 diabetes mellitus become more prevalent below 10 nmol/L. Erectile dysfunction becomes more common at T concentrations below 8 nmol/L.[11,36] Response to T therapy is more likely to be effective in men with progressively lower T values.[37]

Total T measurement is a reasonable test in most clinical situations, but it is important to recognize its limitations. Testosterone bound tightly to sex hormone—binding globulin (SHBG) represents a fraction that is biologically unavailable, whereas T loosely bound to albumin and the unbound fraction bound to proteins (free T) represent bioavailable forms of T. Because of interindividual variation in SHBG concentration, free T concentrations may better reflect the clinical androgen status of some patients.[11]

Furthermore, variable phenotypes of androgen sensitivity exist, mainly owing to variations in the functionality of androgen receptors. One of these is the CAG repeat polymorphism in exon 1 of the *AR* gene. Transcription of androgen-dependent target genes is attenuated in vitro with increasing numbers of triplets. Clinically, androgen response to any serum T concentration (endogenous or in response to T therapy) is reduced as the number of CAG repeats increases.[38-42]

Three key concepts aid understanding the usefulness and limitations of serum T concentrations in men: (1) different intraindividual thresholds exist for various TD symptoms and signs, (2) there is substantial interindividual variability in T thresholds for the same symptom or sign, depending in part on the functionality of the androgen receptor, and (3) variability in SHBG concentrations among individuals influences the concentration of free T for any given total T concentration. Free T measurement can be an important biochemical test in the assessment of men with symptoms consistent with TD.

The diagnosis of TD should include assessment of the entire clinical presentation, aided by biochemical tests. The rigid application of

a uniform total T concentration threshold for all individuals as the primary instrument to diagnose TD lacks a scientific foundation and is discouraged.

RESOLUTION 6. THERE IS NO SCIENTIFIC BASIS FOR ANY AGE-SPECIFIC RECOMMENDATIONS AGAINST THE USE OF T THERAPY IN MEN

Although it is commonly asserted that T levels decline with age, data from the European Male Ageing Study and other sources reveal that age alone is associated with little decline in mean total T levels in men aged 40 years to more than 75 years, with much of the observed decline attributable to comorbidities, including increased BMI.[17] Free and bioavailable T concentrations decline more rapidly than total T levels, in large part due to age-related increase in SHBG. Age is not a specific risk factor for TD, and the term *age-related hypogonadism* is therefore misleading. Most men, even at advanced ages, maintain T levels within the normal reference range. However, comorbidities such as obesity, diabetes, and other chronic conditions are associated with a high prevalence of reduced T levels, often associated with signs and symptoms of TD, irrespective of age.

The clinical and physiologic responses to T therapy have been documented in both younger and older men.[43] Specifically, increases in muscle mass[17] and muscle strength[44] have been reported in younger and older men, while improvement in sexual function is less consistent in older men but is generally positive regardless of age.[19,45,46] Stimulation of erythropoiesis occurs in both younger and older men, but there is an increased risk of erythrocytosis in older men, partly explained by the lower metabolic clearance rate of exogenous T in elderly compared with younger men. With appropriate monitoring, erythrocytosis and other adverse effects can be prevented.[34,47] In light of increased life expectancy and the absence of markedly reduced benefits or a consistent age-related risk profile, we find no justification to recommend restricting T therapy based on age. Moreover, the results of the Testosterone Trials, performed in men aged 65 years and older, confirm significant benefits of T therapy in older men without increased numbers of serious adverse events.[20] Indeed, the number of CV events was identical in the first year of treatment (7 events each in the placebo and T arms) and was higher in the placebo arm after an additional year of follow-up (9 events in the placebo arm, 2 events in T arm). Hospitalizations were also fewer in the T arm.[20]

RESOLUTION 7. THE EVIDENCE DOES NOT SUPPORT INCREASED RISKS OF CV EVENTS WITH T THERAPY

Two recent observational studies reporting increased CV risks with T therapy received intense media attention.[1,2] However, neither provided credible evidence of increased risk. The first underwent 2 official corrections: one for misreporting its results, which actually showed an approximately 50% *lower* absolute rate of adverse CV events in men who received a T prescription compared with untreated men, and the second for large data errors, including that nearly 10% of its all-male database was comprised of women.[16] The second study had no control group, so it is unknown whether CV events (nonfatal MI in that study) differed between treated and untreated men with TD.[16]

In contrast, there has been substantial evidence, accumulated over more than 2 decades, indicating that low T concentrations are associated with increased CV risks and that higher T concentrations appear cardioprotective. Observational studies have revealed increased mortality, atherosclerosis, coronary artery disease, carotid intima-media thickness, and fat mass and impaired glycemic control associated with lower T concentrations.[16,48] Two well-done observational studies reported that T therapy in men with TD was associated with an approximately 50% mortality reduction in T-deficient men.[49,50] In addition, several short-term RCTs have found increased exercise capacity in men with angina,[51] possibly via calcium-mediated coronary vasodilatory effect,[52] and in individuals with heart failure, including one study in women.[16,53] Testosterone therapy has been reported to also improve known CV risk factors, including reduced fat mass, lean body mass, and improved glycemic control.[54-56] The largest meta-analysis of RCTs to date revealed reduced CV events with T therapy in men with metabolic conditions,[57] and another large observational study noted that T therapy was

associated with reduced risk of MI in men in the highest risk category.[58]

In its assessment of CV risks with T therapy, the FDA identified a total of only 4 studies suggesting increased risk, none deemed to provide solid evidence of increased risk.[59] In comparison, more than 100 studies have reported reduced CV risk with higher endogenous T concentration, improvement of known CV risk factors with T therapy, and reduced mortality in T-deficient men who underwent T therapy compared with untreated men. Two recent studies in men who received T therapy found reduced CV events in those whose follow-up T level normalized compared with men whose T concentration remained low.[60,61] There is no credible evidence at this time that T therapy increases CV risk and substantial evidence that it does not. Indeed, there is a strong signal that T therapy may offer CV benefits to men. This merits further investigation. Finally, the evidence indicates that T therapy is not associated with increased risk of venothrombotic events.[62]

RESOLUTION 8. THE EVIDENCE DOES NOT SUPPORT INCREASED RISK OF PCA WITH T THERAPY

Despite a long-standing concern that higher androgen concentrations lead to development of de novo PCa or rapid growth of aggressive PCa, this belief is not supported by the evidence.[6,63] Large prospective longitudinal studies have found no association between endogenous androgen concentrations and PCa risk.[64] Meta-analyses of placebo-controlled T therapy trials have documented no increased risk of PCa in men receiving T therapy.[65] In men who received T therapy, there was no increased risk of high-grade disease.[66,67] Although lowering serum T concentration into the castrate range clearly causes PCa regression and reduces prostate-specific antigen levels, the evidence indicates a limited ability of androgens to stimulate PCa growth, with maximal androgenic stimulation achieved at low T concentrations.[6] For example, exposure to supraphysiologic T doses for up to 9 months failed to increase serum prostate-specific antigen levels or prostate volume in healthy volunteers.[68] This finite ability of androgens to stimulate prostate growth is termed *the saturation model*.[69,70]

There is now strong evidence linking aggressive PCa features to low T concentrations, including high-grade disease, stage at surgery, biochemical recurrence, and progression in men undergoing active surveillance.[63,71] A number of case series have reported low recurrence rates in men with PCa who received T therapy after definitive treatment of localized PCa, including surgical treatment, brachytherapy, and external beam radiation therapy. Two small series have suggested no increased risk of PCa progression with T therapy even in men with untreated PCa undergoing active surveillance.[72,73] A clinical guideline recommendation from the European Association of Urology states that T therapy may be considered after successful treatment of PCa.[74] Although large, long-term studies are lacking, the available evidence does not support increased PCa risk with T therapy.

RESOLUTION 9. THE EVIDENCE SUPPORTS A MAJOR RESEARCH INITIATIVE TO EXPLORE POSSIBLE BENEFITS OF T THERAPY FOR CARDIOMETABOLIC DISEASE, INCLUDING DIABETES

Type 2 diabetes, as well as obesity and the metabolic syndrome, are highly prevalent conditions associated with high rates of morbidity and mortality, including CV mortality.[75] Independent of these conditions, CV events account for approximately 40% of male deaths in industrialized countries. There is a high prevalence of low T levels in men with type 2 diabetes, metabolic syndrome, obesity, and CV disease,[21,76-79] and TD is associated with an adverse CV risk profile and increased atherosclerotic burden.[80]

This association appears to be explained by the relationships linking TD, increased adiposity, insulin resistance, and reduction in lean mass, thus contributing to increased CV risk.[81] A number of small to moderately sized randomized placebo-controlled studies have reported several provocative positive findings, including improved exercise time to ischemia in men with angina,[51] improved exercise capability in men with heart failure,[53,82] improved lipid profile, reduced insulin resistance, and reduced visceral and/or subcutaneous fat.[54,55] Each of these factors is known to influence CV outcomes. In addition, observational studies have found inverse correlations with T for atherosclerosis, incident coronary artery

disease, and mortality.[16] This outcome has been found in community-based populations as well as disease-specific populations, including type 2 diabetes and CV disease in older men. A 6-year retrospective study in T-deficient men with type 2 diabetes found that those treated with T therapy had a 2-fold improvement in survival compared with untreated men.[49] On the basis of known CV risks of TD, beneficial changes in CV risk factors with T therapy, and suggestive data from observational studies in which mortality was reduced with T therapy, the evidence accumulated to date thus argues for performing a placebo-controlled trial of sufficient power to determine whether T therapy improves CV outcomes, particularly in men with diabetes and other metabolic conditions.

DISCUSSION

In the face of considerable public and scientific confusion regarding TD and its treatment, an international expert consensus conference was held to assert, or reassert, fundamental concepts based on the best available evidence and to thereby provide an accurate scientific framework for ongoing and future discussions.

The expert panel vigorously debated 9 resolutions regarding TD and T therapy. These resolutions address key areas, several of which represent foundational concepts that have been challenged recently, others address long-standing areas of concern, and still others represent new areas of controversy. At the conclusion of the discussion period, the final resolutions, as presented in this article, were each accepted unanimously. Of importance, the panel had broad representation by medical specialty and geography, and each participant had extensive clinical or research experience with T or related fields. In many cases, participants were leading figures in their countries or regions on the basis of their acknowledged expertise. Because it is often challenging to reach agreement among experts on any topic, especially a topic as controversial as TD and T therapy, the unanimous support for each of these resolutions may be interpreted as indicating that the science and clinical evidence behind these resolutions is strong and well established, or in the case of negative phrasing (eg, "the evidence does not support…"), that the evidence is clearly lacking or may even support the opposite conclusion.

The importance of a document of this nature is determined greatly by its historical context. In this case, a remarkable degree of media scrutiny has brought intense attention primarily to 2 isolated reports purporting increased CV risk, leading to critical editorials regarding the use of T therapy in the medical and lay press and insertion of new warnings and restrictions by regulatory agencies. In the United States, the concerns regarding the use of T therapy were heightened by widespread television advertising by plaintiff attorneys seeking injury cases in T-treated men for class action lawsuits. Individually and in sum, these reports have given rise to allegations that T therapy is abused and overused and that the increase in T prescriptions has resulted largely from the undue influence of pharmaceutical companies on physician prescribing behavior, including accusations of "disease mongering."[83] Anchored by these 2 reports of CV risk, public criticisms of T therapy have included trivializing the symptoms of TD, questioning the very existence of TD as a condition, asserting that the benefits of T therapy are unproven, and exaggerating the CV and PCa risks associated with treatment. These and other criticisms, together with responses by our expert panel, are presented in Table 2.

This article presents the 9 resolutions agreed upon unanimously by our international expert panel, together with supporting evidence. These resolutions merit perspective and commentary. The first resolution affirmed the large amount of evidence supporting the importance of TD to male health, not only with regard to sexual and nonsexual symptoms but also to general health issues such as obesity, bone density, glycemic control, and even mortality. Public comments that TD does not exist can only be made by individuals without any relevant clinical experience or awareness of the scientific literature. Indeed, there is high-quality evidence that TD is associated with increased all-cause and CV mortality. The impact of TD can be observed around the world; prevalence data reveal that TD is common, regardless of ethnicity or geography.

A curious addition to the T controversy was prompted by the FDA's announcement

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TABLE 2. Common Concerns Regarding Testosterone Deficiency and Testosterone Therapy and Consensus Conference Expert Responses

Concerns regarding TD and T therapy that have appeared in the scientific and lay media	Expert responses
• The condition of low T does not exist	False. *Low T* is an informal term used to describe TD, much as "heart attack" is used in place of myocardial infarction. TD is a well-established medical condition described in all general medical textbooks
• The symptoms of TD do not merit treatment, particularly decreased libido and fatigue	The symptoms of TD are of considerable importance to many affected men. However, decisions regarding treatment must be individualized
• T therapy is risky	All medical treatments entail some degree of risk. Known risks of T therapy include acne, gynecomastia, peripheral edema, infertility, decreased testicular volume, and erythrocytosis. These are reversible with discontinuation of treatment. The evidence fails to support assertions that T therapy is associated with increased CV risk or PCa
• T therapy increases risks of VTE, such as deep venous thrombosis or pulmonary emboli	Available evidence reveals no increased risk of VTE with T therapy[62]
• T therapy increases the risk of myocardial infarction, stroke, and death	Two flawed studies reporting increased CV risk with T therapy received enormous media attention. One misreported primary results[1] and the other[2] had no control/comparison group. In contrast, several dozen studies provide high-level evidence that reduced T concentrations are associated with increased CV events and atherosclerosis, whereas T therapy appears to reduce CV risk or improve known CV risk factors[16]
• T therapy causes PCa to develop or become aggressive	Not supported by evidence. Longitudinal data reveal no relationship between higher serum T level and PCa risk.[64] Meta-analyses found no greater risk of PCa in men who received T therapy compared with placebo.[65] High-grade disease and poor prognostic PCa features are associated with *low* serum T concentrations[63]
• T therapy is experimental/investigational	False. T therapy has been a standard form of medical treatment for men with TD for more than 70 years, with numerous studies documenting benefits and a reasonable safety profile[16,20]
• The decline in T is due to normal aging and does not merit treatment	Age alone has little impact on serum T concentrations. Most of the age-associated decline in serum T levels is associated with development of comorbidities, especially obesity.[17] Many important medical conditions are age related, including coronary artery disease, diabetes, arthritis, cataracts, and most adult cancers. We find no justification to single out TD as a condition that does not merit treatment because it becomes more prevalent with age

CV = cardiovascular; PCa = prostate cancer; T = testosterone; TD = testosterone deficiency; VTE = venothrombotic events.

that T therapy was only indicated in men with one or more specified underlying conditions associated with TD and should not be used for what they termed *age-related hypogonadism*.[8] We found no scientific justification for these recommendations. Specifically, it was reasserted that the symptoms and manifestations of TD are due to inadequate serum T concentrations, regardless of the underlying cause, known or unknown. Over the past 20 years, a number of new causes of TD have been identified, and it is to be expected that others will be identified in the future. We fail to see the logic of restricting treatment to those with identified causes, particularly since many symptomatic men may benefit without a known cause. We note that approximately 80% of individuals with hypertension have no known underlying etiology—an analogous recommendation would be to restrict antihypertensive treatment to only the 20% of patients with known causes of hypertension. This recommendation is illogical and unscientific.

Similarly, the expert panel found no scientific basis for restricting use of an effective treatment because of age alone. There is good evidence that older men respond well to T therapy, as do younger men. Moreover, many of the most commonly treated medical conditions are age related, including erectile dysfunction, decreased libido, diabetes, coronary artery disease, arthritis, and most adult cancers. We find neither evidence nor logic

to support singling out TD as an age-related condition that does not merit treatment.

There is strong, level 1 evidence that T therapy provides benefits for several sexual and nonsexual symptoms related to TD, including erectile dysfunction, decreased libido, and increased fat mass. It is important to recognize that T therapy has a wide range of actions, not all of which have been adequately studied. The lack of definite response in some areas does not diminish the clearly proven efficacy in others, including areas of considerable importance to men. Some studies have reported no sexual benefits with T therapy, such as the study by Basaria et al.[84] Notably, however, their study population was recruited without a requirement for baseline symptoms and included men with normal T concentrations. There is no reason to expect men without symptoms to have symptomatic improvement with treatment, particularly if they do not have true TD. This result is in contrast to that of the recent study by Snyder et al,[20] which found significant benefits of T therapy with regard to erections, libido, and sexual activity. The frequently stated assertion regarding T therapy that "the benefits are unproven" is simply false.

One of the more challenging issues in clinical practice is determining who is a candidate for T therapy based on blood tests for total T. Various professional societies have published clinical guidelines or recommendations that propose a specific threshold below which the diagnosis may be entertained. Yet, there is broad agreement that no specified T threshold reliably separates men with TD from men without TD, nor does it predict who will respond to treatment and who will not. This problem appears to be due to considerable interindividual variability, variability with the bioavailability of T largely based on serum concentrations of SHBG, and genetic variation in numbers of CAG repeats in the *AR* gene, attributed to gene polymorphism, which in turn appears to influence a man's sensitivity to androgens. Awareness of the limitations of total T test results should encourage clinicians to consider clinical signs and symptoms, in addition to biochemical results, in determining who is a candidate for treatment.

For many decades the greatest fear regarding T therapy was that it would promote the development of PCa or precipitate rapid growth of an existing PCa. This fear was based on erroneous interpretations of limited data dating back to 1941.[6] Modern evidence reveals no increased risk of PCa in men receiving T therapy[65] or in men with higher endogenous androgen concentrations compared with lower concentrations.[64] Indeed, there is now a growing body of evidence confirming an association between low T concentrations and poor prognostic features of PCa, such as high Gleason score and biochemical recurrence rates after surgical treatment.[63]

Currently, the most controversial issue regarding T therapy is CV risk. In the substantial literature accumulated over more than 20 years, a total of only 4 studies have reported increased CV risk.[16] Two were severely flawed retrospective studies,[1,2] one a prospective trial with very few (4) major adverse CV events[85] and the other a meta-analysis that included few studies and used CV end points of questionable clinical importance, such as palpitations and nonspecific electrocardiographic changes.[86] The results of this study[86] have been contradicted by at least 6 other meta-analyses that have uniformly concluded that there is no increased CV risk with T therapy.[16] The most recent and largest of these studies noted *reduced* CV events with T therapy in populations of men known to be at high risk due to metabolic conditions.[57]

Of the studies reporting increased CV risk, the one that received the greatest amount of media attention appears to have been performed with substandard scientific rigor, resulting in 2 postpublication corrections.[1] The first was for misreporting its primary data as documenting an increased absolute risk with T therapy, when subsequent review revealed that the absolute risk was reduced by half in men who received T therapy compared with untreated men. The second correction was for large data errors involving more than 1000 patients and for the revelation that nearly 10% of its all-male database was comprised of women. Twenty-nine medical societies and more than 150 leading researchers and clinicians have petitioned for retraction of this article, arguing that these corrections render the study "no longer credible."[87]

In contrast, there are more than 100 studies revealing CV benefits or improved CV risk

factors with T therapy or with higher endogenous T levels.[16] These studies include several small to medium-sized RCTs in men with known heart disease, including angina and heart failure. Moreover, T concentrations are inversely associated with atherosclerosis, incident coronary artery disease, severity of coronary artery disease, carotid intima-media thickness, and mortality. In addition, the single published study designed to investigate thromboembolic events found no increased risk with T therapy.[62]

It has been surprising that the CV risk issue has gained so much credence given the richness of evidence supporting possible CV benefits and the weaknesses of the few articles suggesting risk. This appears to have been a largely media-driven phenomenon, since the science does not support it. In this regard, the American Association of Clinical Endocrinologists and the American College of Endocrinology jointly published their own assessment of the literature, concluding that "there is no compelling evidence that testosterone therapy increases cardiovascular risk."[88] We concur.

Regrettably, the emphasis on increased CV risk with T therapy has masked a critical yet largely unrecognized concept suggested by the accumulated data, namely, that T therapy may offer CV *benefits*. Two observational studies in T-deficient men, one in a US Veterans Administration population[50] and the other in a UK diabetic population,[49] revealed that mortality was reduced by approximately half in those who received T therapy compared with those who did not. Two more recent studies reported reduced CV risk in men whose serum T levels normalized with T therapy compared with men who had persistently low T levels.[60,61] The deleterious effects of increased adiposity and its association with low T concentrations, together with the reductions in fat mass observed with T therapy, provide a solid biological mechanism by which T therapy may be associated with improved CV health and CV outcomes.[16] On the basis of the strongly suggestive evidence that T therapy may provide cardioprotective benefits in men at risk, we believe there is an urgent need for a large prospective controlled clinical trial to assess this possibility.

Several resolutions presented in this article contradict recent positions taken by the FDA.[8] It is worth recognizing that although the FDA plays a critical role in the regulation of pharmacotherapeutics, it does not regulate the practice of medicine. Concepts regarding medical issues require medical expertise, which we have attempted to provide in this consensus document. Our group of experts fully endorses the clinical importance of symptoms and signs for men with TD, a concept promoted in medical guidelines but not embraced so far by regulatory agencies. We find no high-quality evidence to support FDA concerns regarding CV risk with T therapy and, to the contrary, find substantial evidence linking low T concentrations to CV disease and mortality, with suggestive evidence of reduced CV risk with T therapy. Moreover, evidence from the recently published Testosterone Trials has itself undermined several FDA recommendations and provided support for our conclusions.[20] These results include the documentation of major benefits with T therapy, improvement in various TD-related symptoms with treatment, rejection of age-based restrictions on T therapy (men in the Testosterone Trials were all aged 65 years and older), and now level 1 evidence contradicting the assertion that the benefits of T therapy have been adequately confirmed only in men with an identified underlying etiology (classical hypogonadism).[20] One of the more important advances in the field has been identification of the contribution of comorbidities such as diabetes and obesity to TD, which the FDA and other regulatory agencies have so far failed to recognize.

CONCLUSION

An international group of experts has reached the following conclusions: TD is an important medical condition affecting the health and well-being of men; the symptoms of TD result from low levels of T regardless of whether an underlying condition is identified; the impact of TD is global; T therapy is effective, rational, and evidence based; caution must be used in the rigid application of T thresholds in determining who is a candidate for T therapy; there is no basis for restricting T therapy on the basis of age alone; the evidence fails to support increased risks of PCa or CV disease with T therapy; and current evidence supports a major research initiative to explore

possible cardioprotective benefits of T therapy in men with metabolic disease, including diabetes.

Abbreviations and Acronyms: **BMI** = body mass index; **CV** = cardiovascular; **EMA** = European Medicines Agency; **FDA** = Food and Drug Administration; **MI** = myocardial infarction; **PCa** = prostate cancer; **RCT** = randomized controlled trial; **SHBG** = sex hormone–binding globulin; **T** = testosterone; **TD** = testosterone deficiency

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