Critical Update of the 2010 Endocrine Society Clinical Practice Guidelines for Male Hypogonadism: A Systematic Analysis

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Abstract

“Testosterone Therapy in Men With Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline” (Guidelines), published in 2010, serves as an important guide for the treatment of hypogonadal men. Using the Guidelines as a basis, we searched for the most recent level 1 evidence that continues to support the recommendations or provide an impetus to modify all or some of them. We performed a systematic analysis with a PubMed query from January 1, 2010, through March 2, 2015, using the following key words: testosterone/deficiency, testosterone/therapeutic use, cardiovascular, morbidity, mortality, screening, sexual function, lower urinary tract symptoms, obstructive sleep apnea, prostate cancer, fertility, bone mineral density, osteoporosis, quality of life, cognitive, erectile dysfunction, and adverse effects. We identified 17 trials representing level 1 evidence that specifically addressed recommendations made in the Guidelines. Trials examining outcomes of testosterone replacement therapy in men with severe lower urinary tract symptoms and untreated obstructive sleep apnea were identified, potentially refuting the current dogma against treatment in the setting of these conditions. Hypogonadal men with type 2 diabetes mellitus and metabolic syndrome were examined in several trials, demonstrating the beneficial effects of therapy on sexual function and insulin sensitivity. Several trials served as reinforcing evidence for the beneficial effects of testosterone therapy on osteoporosis, muscle strength, and symptoms of frailty. As in the Guidelines, inconsistent effects on quality of life, well-being, and erectile function were also noted in publications. Despite controversies surrounding cardiovascular morbidity and treatment in the setting of prostate cancer, no studies examining these issues as primary end points were identified. The low number of eligible studies since 2010 is a limitation of this analysis.

The annual incidence of hypogonadism is 20% in men in their 60s and 30% in men in their 70s.1 Testosterone replacement therapy (TRT) use in men has risen to 3.75% of US men in their 60s.2 There is a growing need for physicians working in a variety of subspecialties to maintain up-to-date good practices when prescribing TRT. This need was underscored by the recent revelation that of men newly prescribed TRT, only 74.72% had their serum testosterone level measured in the preceding 12 months (from 2001 through 2011).2

In 2010, the Endocrine Society published “Testosterone Therapy in Men With Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline” (Guidelines), which addressed important issues surrounding the diagnosis and treatment of male hypogonadism. This indispensable document provided valuable guidance regarding diagnosis and evaluation of patients with suspected hypogonadism, indications for treatment, information on various available treatment modalities, and recommended monitoring regimens (Supplemental Appendix 1, available online at http://www.mayoclinicproceedings.org). However, since publication of the Guidelines, there have been a variety of high-quality trials that have expanded our understanding of the beneficial and adverse effects of TRT on patients with type 2 diabetes mellitus (DM2), metabolic syndrome (MetS), sexual dysfunction, and frailty. Furthermore, many of the sacrosanct contraindications to TRT have also been reexamined in recent trials, specifically in patients with severe lower urinary tract symptoms (LUTS) and untreated obstructive sleep apnea (OSA).
The recent Food and Drug Administration (FDA) Safety Advisory Board statements regarding TRT are based largely on retrospective data. However, level 1 evidence trials still represent the most accurate assessments of the effects of TRT on all aspects of treatment, including cardiovascular (CV) safety. Thus, we performed a systematic analysis to examine the body of level 1 evidence literature published since 2010 to update various recommendations made in the Guidelines.

**METHODS**

We queried PubMed for articles published from January 1, 2010, through March 2, 2015, using the following search terms: (Testosterone/therapeutic use[MeSH terms] OR testosterone/deficiency [MeSH terms]) AND (cardiovascular OR morbidity OR mortality OR screening OR sexual function OR lower urinary tract symptoms OR obstructive sleep apnea OR prostate cancer OR fertility OR bone mineral density OR osteoporosis OR quality of life OR cognitive OR erectile dysfunction OR adverse effects). The date last searched was March 2, 2015. The manner of the search (the selection and review of studies for inclusion) was performed according to criteria set forth by Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Patient Population, Intervention, Comparator, Outcome, Study Design criteria were used to select trials for inclusion and to define data for extraction (Supplemental Appendix 2, available online at http://www.mayoclinicproceedings.org). As indicated in Supplemental Appendices 1 and 2, the inclusion criteria related to schematized patients covered in the 2010 Guidelines were morbidity and mortality, screening, CV events, OSA, prostate cancer, infertility, bone mineral density (BMD), osteoporosis, sexual function, erectile function, and cognition. Only articles representing randomized, double-blind, placebo-controlled trials (RCTs; evidence level 1a) were selected for review. The abstract query was restricted to published English-language reports of human trials. No restriction was placed on length of clinical follow-up. Data were extracted independently. The risk of bias was systematically assessed for each study on the study level. The principal summary measures included differences in various outcome means or absolute differences when significant differences were encountered, with 95% CIs noted as appropriate.

**RESULTS**

Of an original cohort of 462 abstracts, 26 articles (representing 17 trials) were selected for inclusion (Figure). The potential for bias was assessed and incorporated into the reported findings (Table). On the basis of these findings, we present a critical reassessment of several of the 2010 Guidelines as reflected by recent level 1a evidence trials and outlined herein.

**Contraindications to TRT**

There are several clinical conditions that are either absolute or relative contraindications to TRT, according to the Guidelines. Patients with elevated prostate-specific antigen levels should be referred for urologic consultation before initiating TRT. Furthermore, the Guidelines recommended against TRT in patients with breast or prostate cancer. Similar to the literature underlying the Guidelines, there is an absence of prospective, randomized trials reported after 2010 that
examined these subpopulations. Hence, this current Guidelines statement remains unchallenged by newer high-quality evidence.

The Guidelines also recommended against TRT in patients with untreated severe OSA. Hoyos et al performed a RCT of 67 middle-aged obese men with untreated severe OSA subsequently treated with long-term injectable testosterone undecanoate (TU) for 18 weeks (last injection at 12 weeks). They noted that TRT increased the oxygen desaturation index and the percentage of hypoxemic sleep time only at 7 weeks but not at the final end point. The researchers did not find any differences in apneic episodes or ventilator chemoreflexes. The cohort was composed of only approximately 47% hypogonadal men, a potential source of selection bias. However, even after being controlled for free and total testosterone levels, the results were unchanged. The occurrence of sleep apnea is not commonly monitored as a potential adverse event, but Hildreth et al, in a placebo-controlled trial with testosterone gel in a relatively healthy hypogonadal population, did not observe any instances of worsening Epworth Sleepiness Score (zero events) or daytime hypoxemia (zero events). Therefore, these studies provide the impetus to reexamine this contraindication.

The authors of the 2010 Guidelines also cited severe LUTS as a relative contraindication to TRT. They recommended using a total score greater than 19 on the validated International Prostate Symptom Score (IPSS) questionnaire as a threshold. Perhaps because of this recommendation, severe LUTS is used as an exclusion criterion in many studies, limiting a critical assessment of this recommendation. Research groups led by Hildreth, Del Fabbro, Kenny, Kalinchenko, and Srinivas-Shankar and their coworkers all reported no difference in adverse events vs placebo related to worsening LUTS, as measured by the IPSS, in their cohorts with baseline unreported or mild-to-moderate severity range IPSS. Furthermore, Tan et al, in a trial of 114 hypogonadal men treated with injectable testosterone for 48 weeks, noted that 14.9% of their cohort exhibited baseline severe-range LUTS, as measured by the IPSS, without any difference in prevalence between the 2 treatment arms. The authors actually noted a small improvement in IPSS scores in the TRT arm (mean ± SD effect: 2.41 ± 6.02 for TRT vs 1.62 ± 7.58 for placebo; P = .540), but they did not perform a separate analysis restricted to patients with severe-range LUTS. Although the literature does not yet adequately address severe IPSS specifically, the data seem to refute, or at least challenge, the traditionally held belief that TRT may exacerbate voiding symptoms and suggest that this recommendation may need to be reexamined.

The Guidelines also cited severe, uncontrolled, or poorly controlled congestive heart failure (CHF) as a relative contraindication to TRT. Much like severe LUTS, severe CHF is also often treated as an exclusion criterion to trial enrollment. Nevertheless, Stout et al performed a trial of 41 hypogonadal men with stable CHF treated with injectable testosterone or placebo along with a standardized exercise regimen. The investigators excluded men with decompensated CHF. The mean ± SD baseline
New York Heart Association (NYHA) score was 2.5±0.5 in each treatment arm. Significant improvements in peak oxygen uptake and leg strength were noted in the TRT group. However, compared with placebo, no changes in biometric parameters, inflammatory and cardiac serum markers, or end point NYHA score were observed. Thus, although this trial is of potential interest to men with well-controlled CHF, the specific contraindication against TRT in men with uncontrolled CHF remains unexamined in the literature. Thus, this recommendation should not be challenged.

**Potential Benefits in Men With DM2 or MetS**

In addition to encouraging screening for hypogonadism in men with DM2, the authors of the Guidelines cited conflicting evidence regarding the effects of TRT on insulin sensitivity, biometrics, and sexual and erectile function. However, the Guidelines did not specifically comment on the efficacy of TRT in men with MetS.

Several multicenter, high-quality trials have been published in the interim addressing both of these conditions. The Birmingham, Lichfield, Atherstone, Sutton Coldfield, and Tamworth (BLAST) study in the United Kingdom evaluated 190 symptomatic hypogonadal men with DM2 in an RCT of injectable TU over 30 weeks. The authors noted a very modest improvement in hemoglobin A1c (HbA1c) levels in men without baseline major depression only at 18 weeks (estimated mean difference, −0.18; 95% CI, −0.35 to 0.00; P=.045) but no change in HbA1c levels in men with a diagnosis of major depression. Furthermore, there were no changes in insulin sensitivity, serum insulin levels, or serum inflammatory markers in the overall cohort.

Sexual function and biometrics were also found to be affected by an underlying diagnosis of major depression in BLAST. After excluding men with major depression, the investigators found that patients in the TRT cohort experienced improvements in body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]), weight, and waist circumference (30-week estimated mean changes: BMI, −0.4 kg/m², P=.021; weight, −1.2 kg, P=.038; waist circumference, −1.9 cm, P=.021). Sexual function and symptoms associated with hypogonadism, as measured by the International Index of Erectile Function (IIEF) erectile function domain and the Aging Males’ Symptoms (AMS) scale scores, respectively, were significantly improved in the overall cohort at 30 weeks (estimated mean difference: IIEF erectile function, 2.83 [95% CI, 0.85 to 4.81], P=.005; AMS scale, −2.00 [95% CI, −4.33 to 0.33], P=.092). However, there were no improvements in IIEF erectile function domain or AMS scale scores in men with major depression. These data may be a worthwhile inclusion in the next guidelines.

Another multicenter study, the Testosterone Replacement in Hypogonadal Men With Type 2 Diabetes and/or Metabolic Syndrome (TIMES2) trial, was an RCT evaluating 220 symptomatic hypogonadal men with DM2 or MetS treated with testosterone gel for 12 months. During the first 6-month fixed-dosage phase, insulin sensitivity was significantly improved only in patients with DM2 (homeostasis model assessment-insulin resistance TRT mean reduction, 16.0%; 95% CI, 0% to 29%; P=.049). However, there were no differences in HbA1c levels, fasting plasma glucose levels, and other biometric measurements, such as BMI. Regarding lipids, low-density lipoprotein was improved in patients with MetS only (treatment difference, −0.210; 95% CI, −0.374 to −0.047; P=.012), whereas high-density lipoprotein levels were significantly reduced in patients with DM2 or MetS (treatment difference, −0.049; 95% CI, −0.094 to −0.004; P=.032). No effect on serum triglycerides was observed. Unlike BLAST, the TIMES2 trial revealed significant improvement in overall IIEF scores (treatment difference, 4.886; 95% CI, 0.644 to 9.092; P=.024) but no change in AMS scale scores.

A third multicenter study, conducted by Kalinichenko et al and widely known as the “Moscow” trial, evaluated 184 hypogonadal men with MetS treated with injectable TU for 30 weeks. Their results revealed significant improvements in body weight, BMI, waist circumference, and serum inflammatory markers (change in mean baseline vs 30 weeks: weight, −4.31 kg for TRT vs −0.40 kg for placebo, P<.001; BMI, −1.32 kg/m² for TRT vs −0.11 kg/m² for placebo, P<.001; waist circumference, −6.02 cm for TRT vs −1.46 cm for placebo, P<.001; C-reactive protein 30-week mean, 19 mg/L (180.96 nmol/L for TRT vs 38 mg/L (361.91 nmol/L for placebo, P=.004). Insulin sensitivity and lipid profiles were not significantly improved after 30 weeks compared with baseline.
<table>
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<tr>
<th>Reference, year</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Blinding of outcome assessment</th>
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<th>Other sources of bias</th>
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<tr>
<td>Hoyos et al,7 2012; Killick et al,10 2013</td>
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<td>Low risk; randomization code broken after all data collected and database locked</td>
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<td>Srinivas-Shankar et al,15 2010</td>
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<td>Low risk; assessed by self-report; &gt;85% participants completed</td>
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<td>Low risk; unblinded only once data were locked</td>
<td>Uncertain; ratio of groups experiencing attrition unclear</td>
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<td>Jones et al,20 2011</td>
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<td>Uncertain; 71% compliance (unclear ratio)</td>
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<td>Low risk; double-dummy technique</td>
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<td>Uncertain</td>
<td>Low risk</td>
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<td>Excluded men with total testosterone &lt;1.44 ng/dL, severe LUTS; partially funded by Bayer</td>
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<td>High risk; unblinded if serious adverse event</td>
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<td>Excluded men with elevated IPSS; AMS score/BMI lower in placebo group vs treatment group</td>
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<td>Low risk Low risk; independent assistants</td>
<td>Low risk; preparation of medication packages</td>
<td>Low risk</td>
<td>Low risk; blinded until completion of the placebo-controlled treatment phase; prohibited communication between sites regarding unblinding</td>
<td>Uncertain; overall 81% compliance but uncertain ratio</td>
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<td>Buvat et al., 2011</td>
<td>Low risk Low risk; randomization prepared by manufacturer</td>
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<td>Uncertain; details not provided</td>
<td>Low risk; statistical analysis plan finalized before unblinding</td>
<td>Low risk; compliance in intention-to-treat 78.3% testosterone completed and 79.8% placebo completed</td>
<td>Cutoff value, &lt;400 ng/dL total testosterone or bioavailable testosterone &lt;100 ng/dL; partially funded by Besins International</td>
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<td>Low risk</td>
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<td>Low risk; designated uninvolved physician and pharmacist administered titrations</td>
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<td>Basaria et al., 2010; Basaria et al., 2013</td>
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<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk; adherence &gt;90% in both groups</td>
<td>Gel provided by Auxilium</td>
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<td>Atkinson et al., 2010</td>
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*aHl = apnea-hypopnea index; AMS = Aging Males’ Symptoms; BMI = body mass index; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; TRT = testosterone replacement therapy.

*bSI conversion factors: To convert testosterone values to nmol/L, multiply by 0.0347.
Several single-center RCTs have also examined the effects of TRT on patients with DM2 and MetS. Aversa et al21 performed a trial of men with symptomatic hypogonadism and MetS or DM2 treated with injectable TU for 24 months (blinding terminated early at 12 months) because of significant outcome differences. Insulin sensitivity, serum inflammatory markers, and carotid intima-media thickness were significantly improved in the TRT treatment arm (mean ± SD difference: homeostasis model assessment-insulin resistance, −2.1±0.35 for TRT vs 0.5±0.3 for placebo, P=.001 carotid intima-media thickness, −0.22±0.18 mm for TRT vs 0.05±0.1 mm for placebo, P=.0001). The prevalence of MetS in the TRT arm was reduced; however, this latter analysis was performed after treatment blinding had been stopped at 12 months.21

Gianatti et al,22,23 identified limited anthropometric improvements in a study of TRT in 88 men with well-controlled DM2 and symptomatic hypogonadism treated with injectable TU for 40 weeks. The investigators did not note any significant change in AMS and IIEF scores after treatment. The investigators did not identify any significant changes in insulin sensitivity. There were also no changes in HbA1c level, BMI, or waist circumference. Significant improvements were noted regarding lean body mass (mean adjusted difference, 2078 g; 95% CI, 1519 to 2637 g; P<.001) and abdominal subcutaneous adipose tissue volume (mean adjusted difference, −320 cm³; 95% CI, −477 to −163 cm³; P<.001).22,23

In a smaller crossover design study of 22 men with hypogonadism and DM2 treated with injectable testosterone or placebo for 3 months in random order with a 1-month washout period, Gopal et al24 did not report any effect of TRT on insulin sensitivity, fasting plasma glucose levels, HbA1c levels, lipid levels, or biometric parameters. Therefore, as noted in the Guidelines, evidence supporting improvements in insulin sensitivity in men with DM2 remains inconclusive. However, the new data presented herein identify potentially beneficial effects of TRT in men with MetS. These data may be worthy of inclusion in a subsequent guideline publication.

Effects on Sexual Function, Well-being, and Quality of Life
The Guidelines recommended TRT for men with concomitant hypogonadism, low libido, and erectile dysfunction (ED) after evaluation and treatment with established therapies. However, the Guidelines also noted that the evidence for these recommendations was based on inconsistent trial results. The authors also cautioned that the effects of TRT on quality of life (QoL), underlying major depression, and the efficacy of phosphodiesterase type 5 inhibitor (PDE5I) medications in older men were inconsistent, according to available evidence. However, several recent RCTs addressing these questions have since been published.

Tong et al25 evaluated 120 symptomatic hypogonadal Malaysian men (mean ± SD age, 53.4±7.6 years) treated with injectable TU for 48 weeks. Specifically, the investigators found that overall AMS scale scores were improved in the TRT arm. In addition, results of the 12-Item Short Form Health Survey, a validated questionnaire examining generic QoL, were significantly improved in 5 of 8 domains examined. On multivariate analysis controlling for biometric parameters and baseline AMS scale score, improvements on only 3 domains on the 12-Item Short Form Health Survey (vitality, social functioning, and mental health composite) were statistically significant. A nonsignificant increase (improvement) in the overall IIEF score was also observed (mean ± SD effect, 2.31±4.80 for TRT vs −0.95±4.57 for placebo; P=.130).16,25

Additional studies of the effects of TRT on QoL and other end points were conducted by Pope et al.26 These authors examined 100 hypogonadal men with major depression refractory to selective serotonin reuptake inhibitors. Patients were treated with testosterone gel or placebo for 6 weeks. Ultimately, no effects of TRT on symptoms associated with major depression or QoL, as measured by several validated questionnaires, were noted.26 In a subgroup analysis of men with IIEF data, the authors noted significant improvements in sexual function after TRT (estimated mean difference, 16.8; 95% CI, 7.5 to 26.1; P=.001).27 Thus, hypogonadal men with major depression may benefit from TRT regarding sexual function, but symptoms associated with major depression or overall QoL seem to be unaffected.

Regarding the effects of TRT on mood and well-being, the results remain conflicting, as was originally noted in the 2010 Guidelines. Furthermore, two high-quality studies have
recently examined the effect of TRT on PDE5I efficacy in men with ED. Buvat et al²⁸ performed a multicenter trial (TADTEST) of 173 hypogonadal men with ED who were nonresponders to therapy with the PDE5I tadalafil. Patients were treated with a standardized run-in period of 4 weeks of tadalafil. They subsequently were treated with testosterone gel or placebo in addition to continued tadalafil for 12 weeks. The authors used more liberal inclusion criteria for hypogonadism, the definition of which was based on assays of total testosterone levels (≤400 ng/dL [to convert to nmol/L, multiply by 0.0347]) or bioavailable testosterone levels (≤100 ng/dL). The overall cohort did not exhibit differences between the two treatment arms based on the erectile function domain of the IIEF or the Sexual Encounter Profile diary. However, both primary end points were improved at the 8-week time point, when only men with total testosterone levels of 300 ng/dL or less were analyzed in a separate subgroup (mean ± SD: overall IIEF end point, 11.7±12.4 for TRT vs 2.6±13.4 for placebo, P<.01; Sexual Encounter Profile overall satisfaction, 28.4±32.3 for TRT vs 13.6±33.3 for placebo, P<.1).²⁸

Further evidence disputing the role of TRT in men with ED was reported by Spitzer et al.²⁹,³⁰ The investigators separately examined 140 men with hypogonadism and ED treated with the PDE5I sildenafil during a prerandomization run-in phase. The men were subsequently treated with testosterone gel or placebo for 14 weeks. No significant difference was noted in IIEF erectile function domain or Sexual Encounter Profile scores. Furthermore, validated questionnaires evaluating sexual desire, well-being, mood, and energy also did not reveal significant differences between the two treatment arms.²⁹,³⁰ Thus, the trials identified in the present systematic analysis do not indicate a consistently beneficial role for TRT in hypogonadal men with ED refractory to PDE5I therapy as defined by IIEF scores.

**TRT and CV Morbidity**

The Guidelines cited a meta-analysis from 2005 indicating that there was no difference in the frequency of CV events in men treated with TRT compared with those receiving placebo.³¹ Despite the recent controversy surrounding this subject, there has been a paucity of recent level 1 studies specifically examining the question of CV risk due to TRT. Although not designed with CV morbidity as a primary end point, further post hoc analyses of the Testosterone in Older Men with Mobility Limitation (TOM) study, which was halted prematurely in 2009 after an increase in CV events in the TRT arm, have recently been published.

The TOM trial included 209 men (176 men in the final analysis) older than 65 years with hypogonadism and mobility limitations to be treated with testosterone gel or placebo for 6 months. At baseline, more men in the TRT arm were taking antihypertensive (85% for TRT vs 73% for placebo; P=.04) and lipid-lowering (62% for TRT vs 47% for placebo; P=.03) medications and had been diagnosed as having hyperlipidemia (63% for TRT vs 50% for placebo; P=.05). The incidence of CV-associated adverse events was significantly higher in the TRT arm (23 vs 5 events), even after adjustment for age, BMI, smoking history, lipid parameters, diabetes, hypertension, mobility, and physical performance status. The CV events were quite diverse.

On multivariate analysis of the results of the TOM trial, the posttreatment increase in serum free testosterone level was associated with adverse CV events (10.6 ng/dL; 95% CI, 4.6 to 16.7 ng/dL for CV events vs 5.2 ng/dL; 95% CI, 3.0 to 7.5 ng/dL for no CV events; P=.05). No differences in hematologic parameters were noted between the 2 treatment groups.³²,³³ This study may serve as an important warning sign about the potential dangers of TRT, but the outcomes noted have not been borne out by the other high-quality studies cited in this systematic analysis, including those that specifically examined frail men. Our conclusion is that TRT was not clearly associated with adverse CV events based on the systematic analysis.

**TRT and BMD. Frailty, and Muscle Strength**

The Guidelines noted a modest improvement in BMD at the lumbar spine but not at the femoral neck in patients receiving TRT. The authors described inconsistent findings concerning the effects of TRT on physical function and lower-extremity strength. The evidence analyzed by the authors emerged largely from studies of men without functional limitations.³

Kenny and associates¹³ studied 131 men older than 50 years with hypogonadism, frailty,
and osteoporosis treated with testosterone gel or placebo for 12 months. Lumbar spine BMD increased 3.2% and femoral neck BMD by 1.4% after TRT (each \(P<.05\) vs placebo). Statistically significant, but modest, improvements in total lean body mass were also observed (percentage change, 1.9% for TRT vs 0.3% for placebo; \(P=.027\)). However, no differences were noted in upper- or lower-extremity strength, physical performance, or frailty assessments. In this population of frail men, no difference in adverse events was noted when controlling for baseline characteristics.13

Srinivas-Shankar et al15 also examined a cohort of 274 hypogonadal men with frailty treated with testosterone gel or placebo for 6 months. Of the several strength parameters examined, only isometric knee extension showed significant improvement in patients receiving TRT compared with placebo (mean difference, 8.6 N; 95% CI, 1.3 to 16.0 N; \(P=.02\)). The authors also noted significantly improved gastrocnemius muscle thickness after treatment (treatment effect, 1.4 mm; 95% CI, 0.3 to 2.5 mm; \(P=.015\)). Other measures, including knee flexion, grip strength, and physical function, approached but did not achieve a statistically significant difference. Lean body mass was significantly improved in the treatment arm (mean difference, 1.1 kg; 95% CI, 0.6 to 1.5 kg; \(P<.001\)). Similar to findings from the study by Kenny et al,13 no difference in adverse events was noted in this cohort of frail men.15,34

Other trials have also examined the effects of TRT on physical functioning. Hoyos et al35 in their previously mentioned trial of obese men with OSA treated with TRT for 12 weeks, also did not note a difference in grip strength or most other biometric parameters. Basaria et al,33 in the TOM trial of men with mobility limitations, although largely noted for the CV adverse events, did ultimately demonstrate that the primary end points examining leg press strength, chest press strength, and climbing power were all significantly improved in the TRT group (unadjusted mean differences: leg press strength, 129.8 N, 95% CI, 43.9 to 215.6 N, \(P=.003\); chest press strength, 34.5 N, 95% CI, 13.2 to 55.8 N, \(P=.002\); climbing power with load, 30.2 W, 95% CI, 0.3 to 60.1 W, \(P=.05\)). However, there were no changes in climbing without a carried load or gait speed.32

Del Fabbro et al12 performed an interesting study examining the effects of injectable TRT for 72 days on 29 men with metastatic or locally recurrent cancer, hypogonadism, and moderate-to-severe fatigue. Although the trial was underpowered for their end points, the investigators did note an improvement in Eastern Cooperative Oncology Group score (mean ± SD: 1±0 for TRT vs 0±1 placebo; \(P=.02\)). However, although there was a trend toward improved scores on validated questionnaires examining fatigue, the change was not statistically significant.12 Thus, trials published since 2010 reinforce the positive effects of TRT on BMD and muscle strength, but the effects on the risk of fracture in men with osteoporosis remain unexamined. Thus, the Guidelines remain largely unchallenged.

**DISCUSSION**

The 2010 Guidelines serve as a comprehensive and important tool for the evaluation and treatment of male hypogonadism. However, since their publication, several high-quality, level 1 studies examining contraindications, adverse events, and benefits of TRT have been published. These recent studies have examined specific populations underrepresented in the Guidelines, notably those with frailty and MetS.

There remain significant gaps in the literature, highlighted in the preceding systematic analysis, specifically regarding contraindications to treatment. There is a need for prospective trials addressing men who have been diagnosed as having or having been treated for prostate cancer and their outcomes after TRT. Furthermore, no study has definitively addressed the long-held belief that severe LUTS or uncontrolled CHF are true contraindications to TRT. In addition to contraindications, the recommendation that hypogonadal men undergo periodic bone density scans, underlying the concern for osteoporosis, remains largely unexamined by prospective trials. Further trials similar to that performed by Del Fabbro et al12 examining the specific population of men with cancer and low performance statuses are needed. However, the most pressing need for further high-quality trials remains in the arena of CV morbidity and mortality associated with TRT.

Unfortunately, most of the new influential literature addressing the question of TRT and
associated CV morbidity and mortality has been based on large, retrospective cohorts. Vigen et al.36 published a retrospective study of 8709 men treated in the Veterans Affairs system who were diagnosed as having hypogonadism and who had undergone coronary angiography. The authors noted an increased risk of CV adverse outcomes.36 Finkle et al.37 examined a large health care database composed of 55,593 men to assess the risk of acute nonfatal myocardial infarction within 90 days of filling a testosterone prescription. They noted an increased relative risk for such events in younger men with preexisting heart disease and older men.37

Alternatively, Baillargeon et al.38 performed a retrospective analysis of a Medicare database encompassing 6355 men. The authors did not find an increased risk of myocardial infarction in men prescribed TRT. In fact, they found that TRT use in men in the highest quartile of myocardial infarction risk was associated with a relative reduction of risk of such events.38 However, except for the TOM trial, the level 1 trials cited in the present systematic analysis found no difference regarding CV adverse events compared with placebo treatment, including those focused on frail men.

In light of concerns about CV morbidity associated with TRT, the FDA issued a Safety Announcement on March 3, 2015, cautioning against the use of TRT for hypogonadism due to aging alone and recommended a labeling change to reflect an increased risk of heart attack and stroke. The Safety Announcement stressed that only men with “certain medical conditions” and with hypogonadism that has been confirmed by serum assays should be prescribed TRT. The medical conditions encompass etiologies of hypogonadism restricted to the testes, pituitary gland, or brain. The Safety Announcement further cited the recent FDA Advisory Committee meeting that found a “possible” increased risk of CV events with TRT. Patients either starting or currently prescribed TRT should be advised of these possible risks.4

The Guidelines cautioned against TRT in patients with severe LUTS, uncontrolled/severe CHF, or untreated OSA. One recent trial cast doubt on the effects of TRT on the sleep architecture of patients with untreated OSA.10 Similarly, trials of men with moderate-severity LUTS have not yielded worsening voiding symptoms.15 One trial cited herein examining men with well-controlled CHF noted improvements in discrete physical and strength parameters but no change in NYHA score.17 Again, men with severe-range voiding or CHF diagnoses were excluded, perhaps because of these Guidelines, limiting our ability to critically evaluate them.

Many trials identified in this systematic analysis serve to reinforce the recommendations made by the Endocrine Society authors in 2010. As examples, the contemporary literature reviewed herein reinforces the positive effects exerted by TRT on QoL. The impact of TRT on men with ED refractory to PDE5I therapy remains conflicting. New trials also indicate that TRT may improve BMD in men with osteoporosis, in addition to having largely positive effects on strength and frailty symptoms. Regarding DM2 and MetS, recent studies, such as the TIMES2 and the Moscow trial, noted improvement in insulin sensitivity and several biometric parameters. However, the BLAST trial found no improvement in insulin sensitivity in men with DM2. The several single-center trials cited revealed conflicting results regarding insulin sensitivity. The new trials, thus, do not reflect a major departure from those espoused in the 2010 Endocrine Society Guidelines.

This review has several limitations. The trial inclusion criteria may have overlooked trials that could have further contributed to the conclusions. We did not include any retrospective studies in the analysis, which have been important in the formulation of new FDA recommendations for TRT. Several recent advances, including the possible use of TRT in men with previously treated prostate cancer and new modalities, including selective estrogen receptor modulators, are not included in the analysis because of a lack of level 1 evidence. Finally, the relative lack of new level 1 evidence trials included in this systematic analysis is a limitation.

CONCLUSION

A systematic analysis of level 1 evidence trials examining the safety and efficacy of TRT published since 2010 largely reinforces the Endocrine Society Guidelines. New trials indicate that severe LUTS and untreated OSA may not be absolute contraindications to TRT. Beneficial effects of TRT in men with MetS.
or frailty may be useful additions to future guideline recommendations. There is a lack of high-quality prospective trials examining the effects of TRT on CV morbidity.

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SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: AMS = Aging Males’ Symptoms; BLAST = Birmingham, Lichfield, Atherstone, Sutton Coldfield, and Tamworth; BMI = body mass index; BMD = bone mineral density; CHF = congestive heart failure; CV = cardiovascular; DM2 = type 2 diabetes mellitus; ED = erectile dysfunction; FDA = Food and Drug Administration; Guidelines = ‘Testosterone Therapy in Men With Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline’; HbA1c = hemoglobin A1c; IEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; MetS = metabolic syndrome; NYHA = New York Heart Association; OSA = obstructive sleep apnea; PDE5I = phosphodiesterase type 5 inhibitor; GoL = quality of life; RCT = randomized, double-blind, placebo-controlled trial; TIMES2 = Testosterone Replacement in Hypogonadal Men With Type 2 Diabetes and/or Metabolic Syndrome; TOM = Testosterone in Older Men With Mobility Limitation; TRT = testosterone replacement therapy; TU = testosterone undecanoate

Potential Competing Interests: Dr Seftel is on the editorial board of the Journal of Urology. Dr Niederberger is a member of the American Urological Association Journal of Urology Urological Survey Editorial Committee, is the American Society of Reproductive Medicine co-editor-in-chief of Fertility and Sterility, is the founder and chief technology officer of NextIand, and has received research grant support from Ferring and IBSA.

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