


9:45 – 10:30 am

**Testosterone Replacement Therapy for Hypogonadism:
What is the evidence? Is it safe?**

SPEAKER
Culley C. Carson, MD, FACS



Presenter Disclosure Information

The following relationships exist related to this presentation:

- ▶ Culley C. Carson, MD, FACS: Consultant for AbbVie Inc.; American Medical Systems; and Auxilium. Speaker for American Medical Systems and Auxilium.

Off-Label/Investigational Discussion

- ▶ In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

- Review role of testosterone in Men's Health
- Discuss the diagnosis of Hypogonadism
- Highlight published treatment guidelines for testosterone replacement therapy (TRT)
- Discuss recent data on cardiovascular risk factors for TRT
- Discuss the effects of TRT on the prostate in the aging male

Case Study

- 59-year-old man, retired taxi driver presents for periodic follow up of hypertension
- Type 2 diabetes for 10 yrs
- Fasting glucose between 108 mg/dl and 142 mg/dl
- Hypertension
- Hyperlipidemia
- Erectile dysfunction for 2 years
- Low sexual desire

Case Study – contd.

- **Symptoms**
 - Frequent and easy fatigue
 - Decreased exercise
 - Difficulty concentrating
 - Nocturia
 - Snoring

Case Study – contd.

- **Medications**
 - Glipizide 5 mg bid
 - Metformin 1000 mg bid
 - Atorvastatin 40 mg before bedtime
 - Benazepril 40 mg daily
 - Aspirin 81 mg daily
 - Tadalafil 20 mg prn

Case Study – contd.

• Physical examination

- Height 69 inches, weight 215 lbs (BMI 33)
- Waist circumference 42 inches
- Normal hair distribution
- Genital examination normal, including normal size testicles
- Digital rectal exam: moderately enlarged prostate, no nodules
- No other pathologic signs

Case Study – contd.

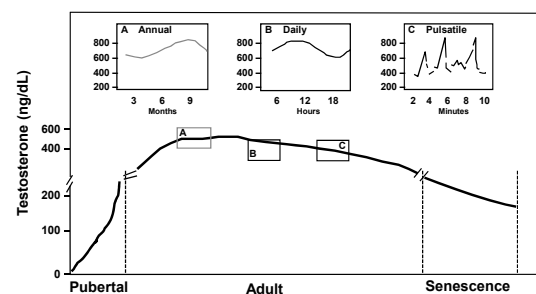
• Labs

- HbA1C 8.2%
- Total cholesterol 143 mg/dl
- LDL cholesterol 93 mg/dl
- Normal blood urea nitrogen and creatinine
- Microalbumin/creatinine in urine <10
- Total serum testosterone 176 ng/dl

Male Hypogonadism

- Endocrine disorder with:
 - Decreased testosterone and/or sperm production
 - Signs and symptoms of androgen deficiency
- Causes of hypogonadism
 - Primary: Testicular defects
 - Secondary: Hypothalamic-pituitary defects
 - Combined (e.g., age-related decline, sickle cell disease)

Plasma Testosterone Levels in Post Pubertal Males



Ewing LL, et al. *Int Rev Physiology*. 1980;22:41-115.

Classical Hypogonadism

- Congenital or acquired causes that may lead to irreversible testosterone deficiencies
 - Primary Hypogonadism
 - e.g., Klinefelter Syndrome, testicular trauma, cryptorchidism
 - Secondary Hypogonadism
 - e.g. Kallman Syndrome, pituitary tumor, prolactinomas

Biochemical Definitions of Hypogonadism

Biochemical Definitions of Hypogonadism*

Guidelines	nmol/l	ng/ml	ng/dl
EAA, ISA, ISSAM, EAU, ASA	Mild <12 Severe <8	<3.40 <2.31	<340 <231
Endocrine Society	<10.4	<3.00	<300
AACE	<7	<2.00	<200

* According to international societies.
AACE = American Association of Clinical Endocrinologists; ASA = American Society of Andrology; EAA = European Academy of Andrology; EAU = European Association of Urology; ISA = International Society of Andrology; ISSAM = International Society for the Study of the Aging Male.
Corona C. & Maggi M. (2009). *Nat Rev Urol*. doi:10.1038/nrurol.2009.235.

Dr Phil's Simple Testosterone Test

According to Dr. Phil, men with a ring finger longer than their index finger, is an indication of higher testosterone levels

Conditions Associated with Testosterone Deficiency

Suggest Evaluation

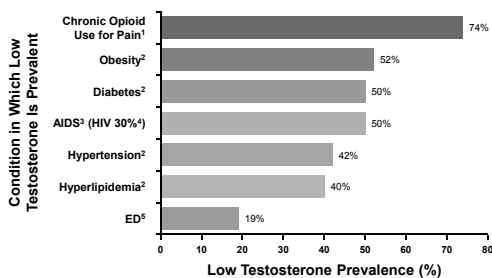
- Sellar mass or irradiation with hypopituitarism
- Conditions with medications (Glucocorticoids, Opioids)
- Cancer therapies – chemotherapy, radiation
- HIV/cancer-associated weight loss
- Infertility
- Osteoporosis/low trauma fracture (young men)

Suggest evaluation in presence of signs/symptoms

- End stage renal disease and maintenance hemodialysis
- Type 2 diabetes mellitus
- Moderate to severe COPD

Bhasin S, et al. *J Clin Endocrinol Metab.* 2010;95(6):2536-2559.

Prevalence of Low Testosterone Other Conditions



ED = erectile dysfunction; HIV = human immunodeficiency virus.

1. Daniell HW. *J Pain.* 2002;3(5):377-384. 2. Mulligan T, et al. *Int J Clin Pract.* 2006;60(7):762-3. Grinspoon S, et al. *Ann Intern Med.* 1998;129(1):18-26. 4. Dobs AS. *Baillieres Clin Endocrinol Metab.* 1998;12(3):379-390. 5. Bodie J, et al. *J Urol.* 2003;169(6):2262-2264.

Signs and Symptoms of Hypogonadism

More Specific

- **Reduced or diminished**
 - Sexual development
 - Libido
 - Spontaneous erections
 - Fertility
 - Secondary sexual characteristics
 - Bone Mineral Density
- **Increased**
 - Fragility fractures
 - Hot flushes, sweats

Less Specific

- **Reduced or diminished**
 - Energy and vitality
 - Mood
 - Concentration and memory
 - Physical performance
 - Muscle bulk / strength
- **Increased**
 - Body fat

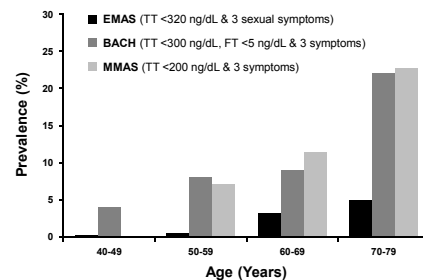
Bhasin S, et al. *J Clin Endocrinol Metab.* 2010;95(6):2536-2559.

Age-Related Decline of Testosterone

- Testosterone decreases 1-2% per year after age 40
- Institute of Medicine (2004): Insufficient data on TRT in elderly men
- Endocrine Society recommends caution in treating older men given paucity of data
- Ongoing T-Trials to characterize benefits in elderly men

Araujo & Wittert. *Best Pract Res Clin Endocrinol Metab.* 2011;25(2):303-19.

Prevalence of Symptomatic Hypogonadism



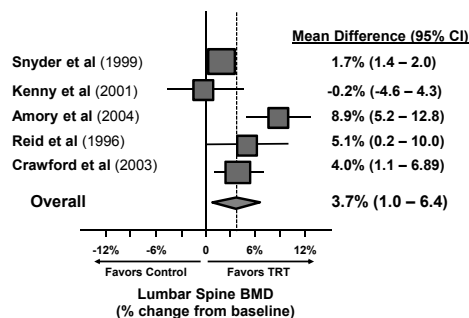
EMAS: Wu, et al. *NEJM.* 2010;363:123-135. BACH: Araujo, et al. *J Clin Endocrinol Metab.* 2007;92(11):4241-7. MMAS: Araujo, et al. *J Clin Endocrinol Metab.* 2004;89(12):5920-6.

TRT Has Potential Benefits in Multiple Body Systems

Potential Benefits

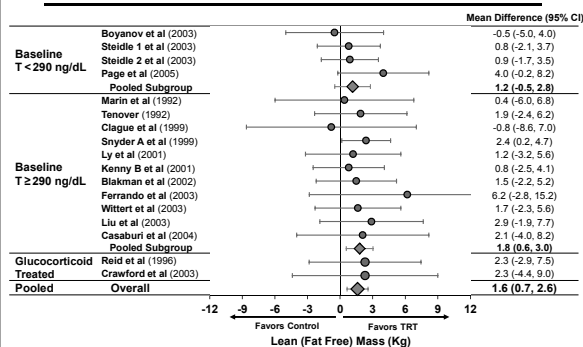
- Bone Mineral Density
- Lean Mass / Fat Mass
- Muscle Strength and Physical Function
- Sexual Function
- Mood
- Fatigue

TRT Improves Bone Mineral Density: Lumbar Spine BMD



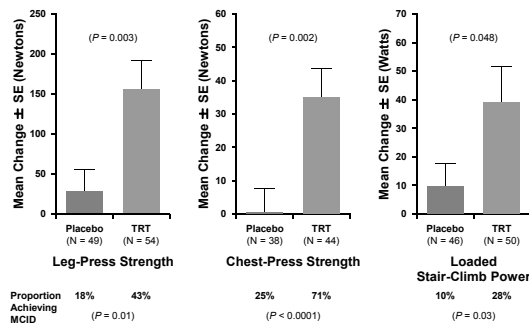
Isidori, et al. Clin Endocrinol. 2005;63:280-93.

TRT Improves Body Composition by Increasing Lean Mass



Isidori, et al. Clin Endocrinol. 2005;63:280-93.

TRT Improved Measures of Muscle Strength & Physical Function in Frail, Older Hypogonadal Men



Basaria, et al. NEJM. 2010;363:109-22. Spitzer, et al. Nature Rev. 2013;9(7):414-24.

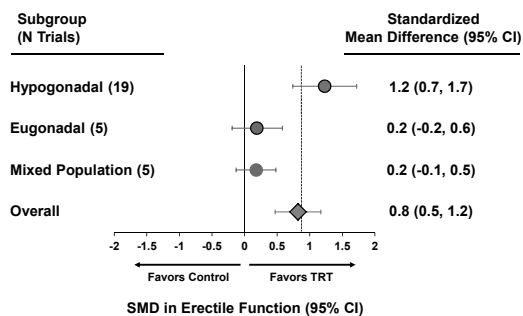
Hypogonadism and ED Intrinsically Tied

- Hypogonadism common in men with ED¹
 - Shared pathophysiology and comorbidities
- Clinicians need to screen and treat simultaneously^{1,2}
- Testosterone combined with PDE5 inhibitors may improve treatment outcomes²
- Chronic PDE5 inhibition improves endothelial function with sustained effect³
 - Rationale for vascular rehabilitation and cardioprotection

ED = erectile dysfunction; PDE5 = phosphodiesterase type 5.

1. Kohler TS, et al. Urology. 2008;71(4):693-697. 2. Corona G, Maggi M. Nat Rev Urol. 2010;7(1):46-56. 3. Aversa A, et al. Int J Impot Res. 2007;19(2):200-207.

TRT Improves Erectile Function in Hypogonadal Men



Corona, et al. J Sex Med. 2014;11:1577-92.

TRT: Mood and Fatigue

• Mood

- Meta-analysis of 16 randomized trials (N=944) of heterogeneous population found moderate overall effect on mood
 - Effect significant in hypogonadal, but not in eugonadal subjects
 - Effect significant in studies with mean age <60, but not ≥60

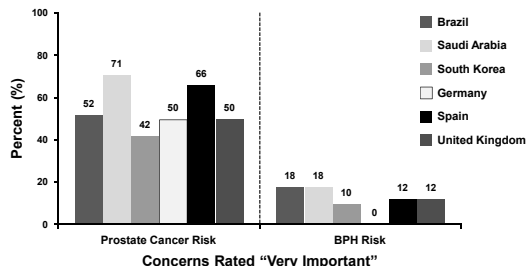
• Fatigue:

- Results vary across studies and patient populations
- Observational study of 799 men treated with testosterone showed a 22% reduction in fatigue scores over 6 months
- In a placebo-controlled study of HIV-infected men, a similar reduction in fatigue scores was observed over 8 weeks

Amanatkar & Chibnall. *Ann Clin Psychiatry*. 2014;26(1):19-32. Rabkin, et al. *J Clin Psychopharm* 1999. Pexman-Fieth, et al. *Aging Male*. 2014.

Physician Concerns about the Prostate in 2006

- Multinational physician survey on testosterone therapy
 - Most common physician concern is prostate cancer risk



BPH = benign prostatic hyperplasia.
Reproduced from Gooren LJ, et al. *Aging Male*. 2007;10(4):173-181.

Testosterone and the Prostate

- Testosterone therapy significantly affects PSA concentrations at low levels of serum testosterone, it does **not** appear to affect prostate size or prostatic testosterone levels
 - Perhaps due to early saturation of androgen receptors within prostate
- **No** evidence that testosterone therapy causes new prostate cancer in hypogonadal men
- To date, 283 men reported in literature have received testosterone therapy after prostate cancer treatment, with low recurrence rates of 1.4%

PSA = prostate-specific antigen.

Historical Origin of Concerns



Conclusion was based on one patient!

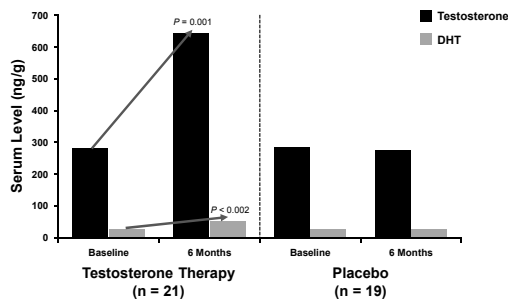
Huggins C, et al. *Cancer Res*. 1941;1:293-297. Reprinted by: *J Urol*. 2002;167(2, pt 2):948-951.

Prostate Cancer and Testosterone Therapy FACTS

- Fear of causing prostate cancer leaves many appropriate patients untreated
- No evidence of causality of testosterone use and development of prostate cancer
- Testosterone will stimulate growth of existing prostate cancers
- Obtain consult for any concern
 - PSA abnormal per guidelines
 - Abnormal prostate exam

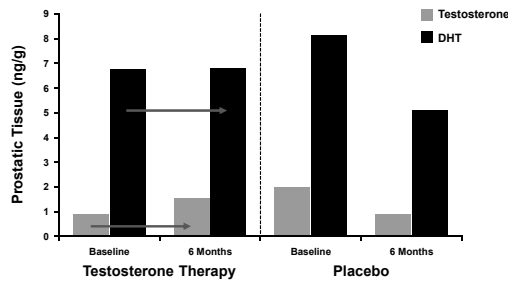
PSA = prostate-specific antigen.
1. Gooren LJ, et al. *Aging Male*. 2007;10(4):173-181. 2. Rhoden EL, et al. *N Engl J Med*. 2004;350(5):482-492. 3. Raynaud JP. *J Steroid Biochem Mol Biol*. 2006;102(1-5):261-266. 4. Wang C, et al. *J Androl*. 2009;30(1): 1-9. 5. Carroll P, et al. *Urology*. 2001;57(2):217-224.

Marks et al: Changes in Serum Androgens



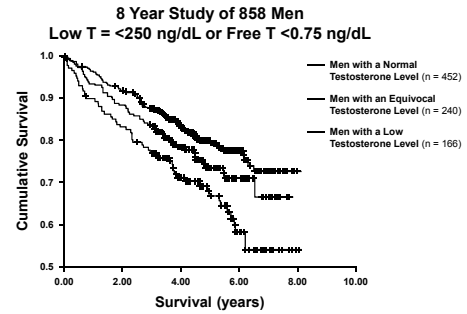
DHT = dihydrotestosterone.
Marks LS, et al. *JAMA*. 2006;296(19):2351-2361.

Marks et al: Changes in Prostate Androgens



These preliminary data suggest that while 6 months of TRT normalizes serum androgen levels, it appears to have little effect on prostate tissue androgen levels and androgen dependent cellular functions

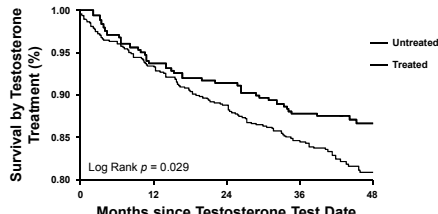
Low Testosterone Associated with Increased Mortality



T = testosterone.
Shores MM, et al. Arch Intern Med. 2006;166:1660-65.

Mortality in Treated vs Untreated Testosterone-Deficient Men in VA Population

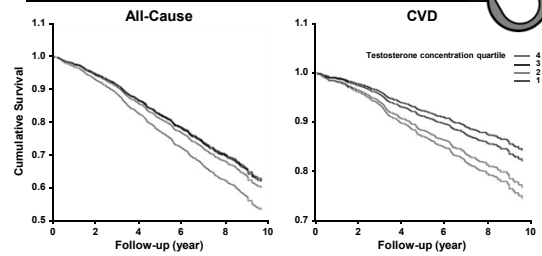
1031 men aged >40 years, T <250 ng/dL
Mortality: 10.3% treated vs 20.7% untreated ($P < 0.0001$)



Subjects at Risk					
	0	12	24	36	48
Untreated	1016	639	557	496	193
Treated	15	301	321	323	146

T = testosterone.
Shores MM, et al. J Clin Endocrinol Metab. 2012;97:2050-58.

Endogenous Testosterone Levels Related to All-Cause and CVD Mortality



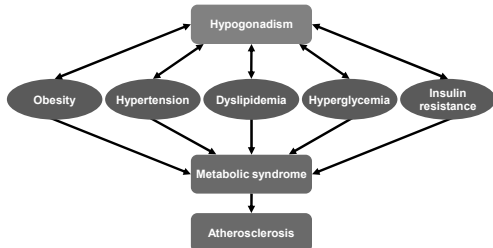
N = 2314 men aged 42-78 y
N = 11,606 men, 2,316 for analysis; 825 men died, 1489 control (no previous cancer or CV disease) Mean fu 7 years

In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes

CVD = cardiovascular disease.
Khaw KT, et al. Circulation. 2007;116(23):2694-2701.

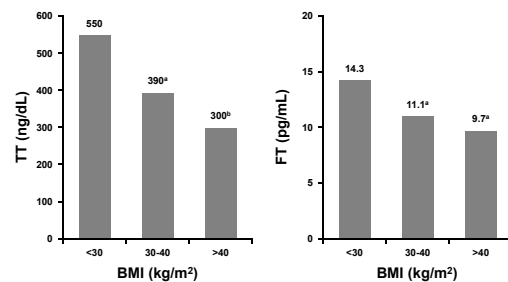
Bidirectional Relationship between Low Testosterone and Metabolic Syndrome Components

- Hypogonadism adversely affects metabolic and cardiovascular risk factors and endothelial function



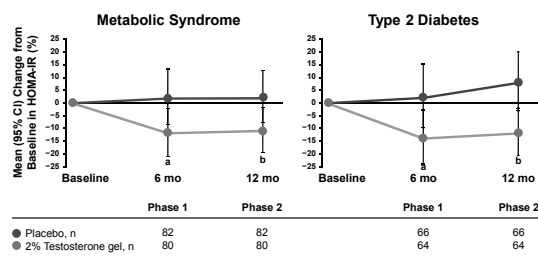
Traish AM, et al. J Androl. 2009;30(1):23-32.

Parallel Decline in TT and FT Levels with Increasing BMI in Men



* $p < .05$, obese vs control. ^b $p < .01$, obese vs control.
BMI = body mass index; FT = free testosterone; TT = total testosterone.
Isidori AM, et al. J Clin Endocrinol Metab. 1999;84(10):3673-3680.

Testosterone Therapy Improves Insulin Sensitivity



Testosterone therapy also improved total cholesterol, LDL, and sexual health

*P=.069, †P=.054.
CI = confidence interval; HOMA-IR = homeostasis model assessment of insulin resistance; LDL = low-density lipoprotein.
Jones TH, et al. *Diabetes Care*. 2011;34(4):828-837.

Mixed Epidemiologic Results in Studies of TRT and Mortality among Men with Low Testosterone

- Vigen et al. (2013)
 - N = 8,709 with testosterone <300 ng/dL
 - Endpoint: all-cause mortality, MI, or stroke
 - Adjusted HR = 1.29 (95% CI: 1.05, 1.58)
- Shores et al. (2012)
 - N = 1,031 with testosterone ≤250 ng/dL
 - Endpoint: all-cause mortality
 - Adjusted HR = 0.61 (95% CI: 0.42, 0.88)

Vigen, et al. *JAMA*. 2013;310(17):1829-36. Shores, et al. *J Clin Endocrinol Metab*. 2012;97(6):2050-8.

Mixed Epidemiologic Results in Studies of TRT and MI among Men with Low Testosterone

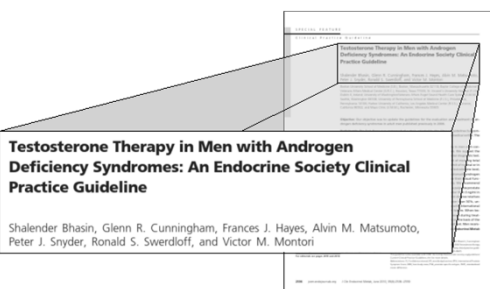
- Finkle et al. (2014)
 - N = 55,593 men on TRT examining non-fatal MI
 - Men ≥65: RR = 2.2 (95% CI: 1.3, 3.8)
 - Men <65 with history of HD: RR = 2.9 (95% CI: 1.5, 5.6)
 - Remaining 80% of cohort: RR = 0.9 (95% CI: 0.6, 1.3)
- Baillargeon et al. (2014)
 - N = 6,355 TRT matched to 19,065 non-TRT controls
 - Men >65: HR = 0.84 (0.69, 1.02)
 - TRT more protective against MI in men at higher MI risk

Finkle, et al. *PLoS ONE*. 2014;9(11):e85805. Baillargeon, et al. *Ann Pharmacother*. 2014;48(9):1138-44.

Recent Epidemiological Studies on TRT and Mortality/CV Outcomes

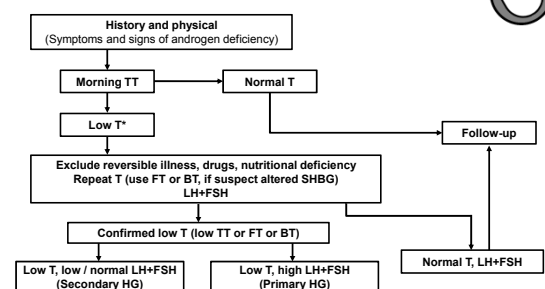
- Limitations
 - Heterogeneity of study populations, intervention duration, and study designs
 - Variable definitions, ascertainment of CV outcomes
 - Unclear treatment indications, treatment regimens, testosterone levels, and exposure
 - Residual confounding
 - Study groups differed in baseline CV risk factors
- Overall Assessment
 - Inconsistent findings across studies
 - Difficult to draw inferences

Expert Guidelines Inform Practice



Reference: Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;95:2536-3559.

Endocrine Society Guidelines: Evaluation of Hypogonadism



Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;95(6):2536-2559.

Testosterone Formulations and Regimens

Testosterone Formulation	Dosage and Frequency	
Injectable		
Testosterone cypionate/enanthate ^{1,2}	Delatesteryl, Depo-Testosterone	50-200 mg every 2 wk
Testosterone undecanoate ^{3,4}		750 mg at baseline, at 4 wk, and every 10 wk thereafter
Implantable		
Testopel		150-450 mg (2-6 pellets) every 3-6 mo (based on clinical experience, 8-12 pellets)
Topical		
Gel ^{5,7}	AndroGel, Fortesta, Testim	1-10 g daily
Axillary solution ⁸	Axiron	30-120 mg daily
Patch system ⁹	Androderm	2 or 4 mg daily
Buccal		
Buccal system ¹⁰	Striant	30 mg every 12 h
Oral		
Oral ^{11,a}	200 mg twice daily T Undecanoate self-emulsifying drug delivery system	

¹In development in United States.
²http://www.accessdata.fda.gov/drugatfda_docs/label/2007/009165s031b1.pdf. ³<http://www.nlm.nih.gov/medlineplus/druginformeds/a014041.html>.
⁴Morganster A, et al. *J Urol*. 2008;180(6):2307-2313. ⁵<http://www.nlm.nih.gov/medlineplus/druginformeds/a014041.html>. ⁶<http://www.fda.gov/downloads/Drugs/DrugSafety/UCM255313.pdf>. ⁷<http://www.fda.gov/downloads/Drugs/DrugSafety/UCM255313.pdf>. ⁸<http://www.fda.gov/downloads/Drugs/DrugSafety/UCM255313.pdf>. ⁹http://www.accessdata.fda.gov/drugatfda_docs/label/2009/021454a00b1.pdf. ¹⁰<http://www.fda.gov/downloads/Drugs/DrugSafety/UCM249398.pdf>. ¹¹http://www.accessdata.fda.gov/drugatfda_docs/label/2006/020489b013b1.pdf. ¹²http://www.accessdata.fda.gov/drugatfda_docs/label/2004/021543s0202.pdf. ¹³Yin AY, et al. *J Androl*. 2012;33(2):190-201.

Endocrine Society Guidelines: Monitoring of TRT

	Baseline	Each Visit	3-6 Months	Annually	1-2 Years
Symptom response		X	X	X	
Adverse events		X	X	X	
Testosterone levels	X		X		
Hematocrit	X		X ^a	X	
BMD of lumbar spine / femoral neck					X ^b
Digital rectal exam/PSA	X		X ^c		

^aIf hematocrit >54%, stop therapy until hematocrit decreases to safe level; evaluate patient for hypoxia and OSA; reinstate therapy at lower dose. ^bFor patients with osteoporosis or low trauma fracture, consistent with regional standard of care. ^cAfter 3-6 months, perform in accordance with guidelines for prostate cancer screening, depending on age and race of patients. Obtain urological consultation under certain conditions.
 Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;95(6):2536-2559.

Summary of 2010 Endocrine Guidelines

Do
Not
Treat

- Patients with breast or prostate cancer
- A palpable prostate nodule or induration
- Abnormal PSA
- Consider consultation in high risk patients
- Patients with erythrocytosis
- Untreated severe sleep apnea
- Severe lower urinary tract symptoms with International Prostate Symptom Score > 19
- Uncontrolled or poorly controlled heart failure

Bhasin S, Cunningham GR, Hayes FJ, et al. *J Clin Endocrinol Metab*. 2010; 96(6): 2536-2559.

Conclusions: Benefits Determined by Patient Selection

- TRT is well accepted in men with classical signs/symptoms & etiologies of hypogonadism
- Select chronic diseases & medications result in suppression of the H-P-G axis (e.g. opiates, radiation therapy) & may lead to symptoms & consideration of treatment
- Poorly defined, mild reductions from chronic disease & aging should be a risk-benefit discussion with frequent re-evaluations