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Presenter Disclosure

Speaker’s Bureau: None
Which Men should receive Testosterone?

- Symptoms and signs consistent with hypogonadism
  
  AND

- Unequivocally low morning serum testosterone concentration
- Morning: 8-10AM best
- Confirmed: at least two values consistently low

- Source: Various Guidelines
Causes of Low Testosterone

**Congenital**

- Klinefelter syndrome & variants (1/400*)
- Kallmann syndrome (1/10,000*)
- Hemochromatosis
- Cryptorchidism (8/1000*)
- Defects in androgen synthesis or action

**Acquired**

- Pituitary disorder
- Testicular trauma
- Autoimmune syndromes
- Medications (corticosteroids, Ketoconazole, opioids)
- Aging
- Obesity and Type 2 Diabetes
- Severe systemic illness: HIV/AIDS
- Chronic renal failure
- COPD/Respiratory illness
F.D.A. recommendation on 3rd March, 2015

- Testosterone is an F.D.A.-approved replacement therapy only for men with disorders of the testicles, pituitary gland or brain that cause hypogonadism.
- It should not be used to relieve symptoms in men who have low testosterone for no reasons other than aging.
- Is testosterone therapy by most prescribers use or misuse?
Caution about TRT in Older men

- Clinicians should consider offering testosterone therapy on an individualized basis to older men with consistently low testosterone levels on more than one occasion and significant symptoms of androgen deficiency, after appropriate discussion of the uncertainties of the risks and benefits of testosterone therapy in older men.

- The baseline prevalence of disorders such as prostate cancer, benign prostatic hypertrophy, and congestive heart failure that might be exacerbated by testosterone administration is high in older men; therefore, small changes in risk in either direction could have enormous public health impact.

Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline, *J Clin Endocrinol Metab*, 2010
IMPLICATIONS of FDA recommendations?

- There is NO evidence that response to testosterone replacement therapy is dependent upon the cause of hypogonadism.

- Since there is no meaningful definition of aging, will restrictions apply to middle-aged individuals, as well? It has been well documented that the decline in testosterone concentrations is continuous across the life span of men beyond the age of 30 years.

- How will “older” patients who are currently on long-term therapy and have experienced demonstrable improvement of quality of life be persuaded to discontinue therapy?
Decline in Testosterone with age

Total testosterone levels vary by age

Free testosterone levels vary by age

Study design:
In a study to establish reference ranges for total testosterone (TT) and free testosterone (FT) in a community-based sample of men, TT was measured using liquid chromatography tandem mass spectrometry in nonobese healthy men, aged 19-40 yrs, in the Framingham Heart Study (FHS) Generation 3. FT was calculated. Values below the 2.5th percentile of reference sample were deemed low. The association of low TT and FT with physical dysfunction, sexual symptoms (European Male Aging Study [EMAS] only), and diabetes mellitus was determined in three cohorts: FHS Generations 2 and 3, EMAS, and the Osteoporotic Fractures in Men Study (MFOS).

Reference:
MORE SPECIFIC symptoms and signs suggestive of androgen deficiency in men

- Incomplete or delayed sexual development, eunuchoidism
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small (especially 5 ml) or shrinking testes
- Inability to father children, low or zero sperm count
- Height loss, low trauma fracture, low bone mineral density
- Hot flushes, sweats

Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline; J Clin Endocrinol Metab, June 2010, 95(6):2536–2559
LESS SPECIFIC symptoms and signs suggestive of androgen deficiency in men

- Decreased energy, motivation, initiative, and self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic)
- Reduced muscle bulk and strength
- Increased body fat, body mass index
- Diminished physical or work performance

Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline; *J Clin Endocrinol Metab*, June 2010, 95(6):2536–2559
The Syndrome of Late-Onset Hypogonadism

as defined by at least
• three sexual symptoms
  and
• total T of <320 ng/dl
  and
• free T of <6.3 ng/dl

Tajar et al; J Clin Endocrinol Metab, April 2010, 95(4):1810–1818
Diurnal Rhythms in Serum Testosterone in Normal Males

Mean bioavailable testosterone concentrations (± SEM) without (black square) or with a standard meal (white square) containing a total energy of 550 kcal (28% protein, 26% fat and 46% carbohydrates). (n = 11).

No change in LH or SHBG but a decline of 30% in testosterone from 60 to 120 min after food intake compared to samples taken in the fasting state.

Lehtihet et al, Andrologia 2012
CLINICAL EVALUATION OF PATIENTS WITH HYPOGONADOTROPIC HYPOGONADISM

- Total testosterone should be measured by liquid chromatography tandem mass spectrometry
- Free Testosterone should be separated by equilibrium dialysis
- Calculated Free Testosterone (using total testosterone, SHBG and albumin) is also reliable (normal range 6.5-25 ng/dl)

http://www.issam.ch/freetesto.htm

How much testosterone should be given during replacement therapy?

- When TRT is initiated, the therapeutic target should be to raise serum T level into a range that is mid-normal for healthy young men.

- What is the normal range? Should we have age-specific normal ranges?


## Normal range of Total and Free Testosterone concentrations

<table>
<thead>
<tr>
<th>Young (19-40 years) healthy non-obese men (n=456) (Framingham Study Cohort)</th>
<th>Elderly (70-89 years) healthy men (n=394) Health in Man Study (Australia)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Testosterone (ng/dl)</strong></td>
<td><strong>Total Testosterone (ng/dl)</strong></td>
</tr>
<tr>
<td><strong>Free Testosterone (ng/dl)</strong></td>
<td><strong>Free Testosterone (ng/dl)</strong></td>
</tr>
<tr>
<td><strong>2.5th percentile</strong></td>
<td>348</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
<tr>
<td><strong>97.5th percentile</strong></td>
<td>1197</td>
</tr>
<tr>
<td></td>
<td>23</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>724 (221)</td>
</tr>
<tr>
<td></td>
<td>14.2 (4.5)</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>699</td>
</tr>
<tr>
<td></td>
<td>13.4</td>
</tr>
</tbody>
</table>

Total testosterone was measured using LC-MS/MS. Free testosterone was calculated using SHBG and albumin.

Bhasin et al; J Clin Endocrinol Metab, August 2011, 96(8):2430–2439
Yeap et al, J Clin Endocrinol Metab, November 2012, 97(11):4030–4039

Healthy older men were those reporting excellent or very good health and who also had no history of smoking, diabetes, CVD, cancer, depression, or dementia.
Probability of dying from any cause according to plasma levels of Testosterone in elderly men (3690 community-dwelling men aged 70 to 89 years)

optimal range of circulating total T: 282–455ng/dL

Testosterone-Replacement Therapy Potential Benefits

- Improved libido
- Positive effects on fatigue
- Increase in lean body mass and strength
- Decrease in body fat mass
- Improved bone mineral density
  (effects on fracture risk are currently unknown)

Results after 36 Months of Testosterone Gel Therapy: Sexual Function

Effects of Testosterone Treatment in Older Men

for the Testosterone Trials Investigators*
A Sexual Activity

Change from Baseline in PDQ-Q4 Score

Month

No. at Risk
Testosterone 230 205 208 205 193
Placebo 229 198 189 190 193

P<0.001
These data do not support the routine addition of testosterone to a PDE5 inhibitor therapy to improve erectile response in men with ED and low testosterone levels.
Results after 36 Months of Testosterone Therapy: Bone Mineral Density

Change Hip BMD

Change Spine BMD

No trial has reported effect of testosterone replacement on fracture incidence. TRT is not a treatment for osteoporosis.

Figure 3. Effects of Testosterone or Placebo Treatment for 12 Months on Volumetric Bone Mineral Density and Estimated Bone Strength of Trabecular, Peripheral, and Whole Bone of the Spine and Hip, as Assessed by Quantitative Computed Tomography
Pathways of Testosterone Action

LH

- Amplification Pathway (prostate, skin)
  - 5α-reductase (5-10%)
  - DHT
  - Androgen receptor

- Direct Pathway (muscle)
  - Androgen receptor

- Diversification Pathway (brain, bone)
  - Estradiol
  - Estrogen receptor

- Inactivation Pathway
  - Hepatic oxidation & conjugation
  - Renal excretion

Testosterone 5-7 mg/day

Steroid Synthesis Pathway

- Cholesterol
  - pregnenolone
  - Progesterone
  - 17-OH-pregnenolone
  - 17-OH-pregnenolone
  - DHEA
  - Androstenedione
  - Androstenediol
  - Testosterone

FIGURE 1. Pathway for testosterone synthesis. (DHEA = dehydroepiandrosterone)
Treatment with 1mg anastrazole or placebo in elderly hypogonadal men for one year (JCEM 2009)
Treatment with 1mg anastrazole or placebo in elderly hypogonadal men for one year: effect on bone mineral density (JCEM 2009)
Results after 36 Months of Testosterone Therapy: Effect on Body Composition

Lean Body Mass Change

Fat Body Mass Change

Cohort 1: 198 healthy men 20 to 50 years of age were given goserelin acetate (to suppress endogenous testosterone and estradiol) and were randomly assigned to receive a placebo gel or 1.25 g, 2.5 g, 5 g, or 10 g of testosterone gel daily for 16 weeks.

Cohort 2: 202 healthy men received goserelin acetate, placebo gel or testosterone gel, and anastrozole (to suppress the conversion of testosterone to estradiol).

Finkelstein et al, NEJM 2013
A Percentage of Body Fat

Cohort 1 vs. cohort 2 interaction, P<0.001

B Total-Body Lean Mass

Cohort 1 vs. cohort 2 interaction, P=0.22

C Subcutaneous-Fat Area

Cohort 1 vs. cohort 2 interaction, P=0.029

D Intraabdominal-Fat Area

Cohort 1 vs. cohort 2 interaction, P=0.021
Changes from baseline in FFM, fat mass, leg press strength, and skeletal muscle mass in
• young (black bars) and
• older (grey bars) men in response to graded doses of testosterone enanthate.
Healthy, young (n=54) and older men (n=52) were randomized to receive a long-acting GnRH agonist plus one of five different doses of testosterone enanthate (25, 50, 125, 300, and 600 mg weekly, im) for 20 wk.

The Testosterone in Older Men with Mobility Limitations (TOM) trial

Changes in gait speed without a load and stair-climbing power without a load did not differ significantly between the groups. Basaria et al, NEJM, 2010
Testosterone Replacement Therapy Recommended Dosing and Administration

**Intramuscular**
- Testosterone enanthate or cypionate
  - 75-100 mg weekly or 150-200 mg every 2 weeks
  - Long acting testosterone undecanoate 750mg 5 times a year

**Transdermal Gels (Androgel 1% and 1.62%, Testim 1%, Fortesta 2%, Vogelxo 1%)**
  - applied daily

**Transdermal underarm solution (Androxal)**
  - 60 mg (30mg under each arm) daily

**Transdermal Patches (Nonscrotal)**
  - 2.5-7.5 mg applied nightly for 24 hours

**Pellets**
  - 150-450 mg implanted subcutaneously every 3-6 months

**Buccal bioadhesive testosterone tablets (Striant)**
  - 30 mg twice a day, alternating sides of the mouth above the incisor teeth

**Intranasal testosterone gel**
  - 11 mg three times a day
Intramuscular
- Peaks and valleys in serum T levels
- Fluctuation in mood or libido
- Pain at injection site
- Pulmonary oil embolism (T undecanoate)

Transdermal Patches
- Skin irritation at application site (20%)

Buccal patches
- Absorbed from buccal mucosa
- Gum irritation (18%)

Transdermal Gels and solution
- Risk for transference to others
- Cannot use if allergic to topical alcohol preparations
- Flammable

Intranasal testosterone
- Nasal discomfort (6%)

Pellets
- Infection
- Pellet expulsion
Treatment of HH with Clomiphene

Observational trial of 46 patients (mean age 44 years); 75% of patients were on 25mg of clomiphene every other day at 36 months. Moskovich et al, BJU Int 2012 Nov
Enclomiphene, Testosterone and sperm count

129 overweight men, aged 18–60 years, with secondary hypogonadism were randomized to receive enclomiphene, androgel and placebo in a double-dummy design (gel and capsule): phase III study.

• Early morning serum TT levels ≤300 ng/dL and had low or normal LH (<9.4 IU/L) levels measured on two separate occasions 2-10 days apart.

• At week 4, the men who did not achieve a TT of >450 ng/dL on 12.5 mg enclomiphene citrate were up-titrated to 25 mg enclomiphene citrate. Androgel 1.62% was also titrated.

BJU Int, 2016
Men provided semen samples twice at baseline and twice at the end of the study.

<table>
<thead>
<tr>
<th>% of men with oligospermia (&lt;15 million/ml)</th>
<th>Enclomiphene</th>
<th>Testosterone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>49</td>
<td>4</td>
</tr>
</tbody>
</table>
PSA and Testosterone

- Does Testosterone replacement increase PSA? 
  ~30%; increases PSA to normal levels. An average increase in serum PSA levels of about
  - 0.30 ng/ml in young hypogonadal men
  - 0.43 ng/ml in older hypogonadal men

- Does Testosterone increase prostate volume? 
  ~15%
PSA in untreated hypogonadal men (n=47), testosterone-treated hypogonadal men (n=78), and age-matched normal men (n=75)

Behre et al. Clin Endocrinol 1994
PSA concentrations in older men with low T who were treated with either T (T-only), T and Finasteride (T+F), or placebo for 36 months

The saturation model suggests that testosterone is “like water for a thirsty tumor.” Once thirst is quenched, additional water serves only as excess. The saturation point occurs at approximately 8 nmol/l (approximately 250 ng/dl)
Fig. 1 Serum testosterone and risk of prostate cancer (dose-response meta-analysis). EHPCCG, Endogenous Hormones and Prostate Cancer Collaborative Group; RR, relative risk; SRR, summary relative risk.

<table>
<thead>
<tr>
<th>Study</th>
<th>Weights</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller, 2012</td>
<td>32.52%</td>
<td>1.02 [0.97, 1.07]</td>
</tr>
<tr>
<td>Daniels, 2010</td>
<td>4.91%</td>
<td>1.02 [0.91, 1.15]</td>
</tr>
<tr>
<td>Gill, 2010</td>
<td>6.82%</td>
<td>0.95 [0.86, 1.05]</td>
</tr>
<tr>
<td>Weiss, 2008</td>
<td>5.96%</td>
<td>1.07 [0.97, 1.20]</td>
</tr>
<tr>
<td>Travis, 2007*</td>
<td>2.61%</td>
<td>1.00 [0.85, 1.18]</td>
</tr>
<tr>
<td>Severi, 2006*</td>
<td>3.86%</td>
<td>1.00 [0.88, 1.14]</td>
</tr>
<tr>
<td>Parsons, 2005*</td>
<td>0.39%</td>
<td>1.07 [0.71, 1.63]</td>
</tr>
<tr>
<td>Platz, 2005*</td>
<td>1.88%</td>
<td>0.97 [0.80, 1.17]</td>
</tr>
<tr>
<td>Ozasa, 2004*</td>
<td>0.21%</td>
<td>1.11 [0.63, 1.96]</td>
</tr>
<tr>
<td>Stattin/Finnland, 2004*</td>
<td>1.37%</td>
<td>1.06 [0.85, 1.32]</td>
</tr>
<tr>
<td>Stattin/Norway, 2004*</td>
<td>12.29%</td>
<td>0.93 [0.86, 1.00]</td>
</tr>
<tr>
<td>Stattin/Sweden, 2004*</td>
<td>11.30%</td>
<td>0.96 [0.89, 1.04]</td>
</tr>
<tr>
<td>Chen, 2003*</td>
<td>5.98%</td>
<td>0.96 [0.86, 1.07]</td>
</tr>
<tr>
<td>Heikkila, 1999*</td>
<td>2.40%</td>
<td>1.02 [0.86, 1.20]</td>
</tr>
<tr>
<td>Dorgan, 1998*</td>
<td>1.05%</td>
<td>0.87 [0.68, 1.12]</td>
</tr>
<tr>
<td>Vatten, 1997*</td>
<td>0.74%</td>
<td>0.95 [0.70, 1.28]</td>
</tr>
<tr>
<td>Gann, 1996*</td>
<td>2.34%</td>
<td>1.08 [0.91, 1.28]</td>
</tr>
<tr>
<td>Nomura, 1996*</td>
<td>1.30%</td>
<td>1.00 [0.80, 1.26]</td>
</tr>
<tr>
<td>Hsing, 1993*</td>
<td>1.31%</td>
<td>1.09 [0.87, 1.37]</td>
</tr>
<tr>
<td>Barrett–Connor, 1990*</td>
<td>0.76%</td>
<td>1.00 [0.74, 1.35]</td>
</tr>
</tbody>
</table>

SRR 0.99 [0.96, 1.02]

*: study included in EHPCCG pooled analysis

Heterogeneity: $I^2 = 0\%$ [0%; 19%]; $Q = 12.20$, df = 19 ($p = 0.88$)

Publication bias: Begg = 0.16 ($p = 0.87$); Egger = −0.79 ($p = 0.17$);
Macaskill = −0.41 ($p = 0.69$)
Testosterone replacement therapy and risk of prostate cancer. OR, odds ratio.

<table>
<thead>
<tr>
<th>Study</th>
<th>Weights</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hackett, 2013</td>
<td>6.62%</td>
<td>0.34 [0.01, 8.56]</td>
</tr>
<tr>
<td>Behre, 2012</td>
<td>6.64%</td>
<td>2.79 [0.11, 68.88]</td>
</tr>
<tr>
<td>Basaria, 2010</td>
<td>6.62%</td>
<td>3.07 [0.12, 76.32]</td>
</tr>
<tr>
<td>Kenny, 2010</td>
<td>6.57%</td>
<td>2.66 [0.11, 66.83]</td>
</tr>
<tr>
<td>Srinivas-Shankar, 2010</td>
<td>6.63%</td>
<td>0.35 [0.01, 8.57]</td>
</tr>
<tr>
<td>Emmelot-Vonk, 2008</td>
<td>7.36%</td>
<td>0.19 [0.01, 4.03]</td>
</tr>
<tr>
<td>Marks, 2006</td>
<td>24.12%</td>
<td>0.44 [0.08, 2.38]</td>
</tr>
<tr>
<td>Nair, 2006</td>
<td>6.51%</td>
<td>0.37 [0.01, 9.46]</td>
</tr>
<tr>
<td>Amory, 2004</td>
<td>14.98%</td>
<td>1.88 [0.22, 15.94]</td>
</tr>
<tr>
<td>Steidle, 2003</td>
<td>7.37%</td>
<td>1.76 [0.08, 37.07]</td>
</tr>
<tr>
<td>Snyder, 1999</td>
<td>6.57%</td>
<td>2.94 [0.12, 73.94]</td>
</tr>
</tbody>
</table>

**SOR – All studies**

Heterogeneity: $I^2 = 0\%$ [0%; 25%]; $Q = 5.29$, df = 10 ($p = 0.87$)
Publication bias: Begg = 0.23 ($p = 0.82$); Egger = 0.93 ($p = 0.26$); Macaskill = 0.40 ($p = 0.70$)
**Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis;** Fernandez-Balsells et al, JCEM 2010

<table>
<thead>
<tr>
<th>Dichotomous outcomes</th>
<th>RR</th>
<th>Lower boundary</th>
<th>Upper boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite prostate endpoint</td>
<td>1.41</td>
<td>0.93</td>
<td>2.14</td>
</tr>
<tr>
<td>Impaired Urinary flow</td>
<td>0.86</td>
<td>0.13</td>
<td>5.53</td>
</tr>
<tr>
<td>PSA levels &gt;4 ng/ml</td>
<td>1.22</td>
<td>0.67</td>
<td>2.21</td>
</tr>
<tr>
<td>Significant increase in PSA (&gt;1.5 ng/ml)</td>
<td>1.56</td>
<td>0.87</td>
<td>2.80</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>3.15</td>
<td>1.56</td>
<td>6.35</td>
</tr>
<tr>
<td>Continuous outcomes</td>
<td>Weighted mean difference</td>
<td>Lower boundary</td>
<td>Upper boundary</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.8</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>3.2</td>
<td>1.4</td>
<td>5.0</td>
</tr>
<tr>
<td>Prostate symptom scale</td>
<td>0.3</td>
<td>-0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>PSA change (ng/ml)</td>
<td>0.10</td>
<td>-0.01</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mg/dl)</strong></td>
<td><strong>-0.5</strong></td>
<td><strong>-0.9</strong></td>
<td><strong>-0.1</strong></td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>0.3</td>
<td>-4.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Fasting triglycerides (mg/dl)</td>
<td>-11</td>
<td>-27</td>
<td>4</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>-1</td>
<td>-6</td>
<td>4</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.20</td>
<td>-0.02</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>2</td>
<td>-2</td>
<td>5</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.6</td>
<td>-5.2</td>
<td>4.0</td>
</tr>
</tbody>
</table>
Association of Testosterone Levels With Anemia in Older Men. The T trials. *JAMA Intern Med 2017*
Evaluate patient 3-6 months after testosterone initiation, then annually for response to treatment and symptom resolution.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3-6 Months</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Concentrations</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PSA and DRE Age &gt;40 years</td>
<td>✔</td>
<td>✔</td>
<td>In accordance with prostate cancer screening guidelines, depending on the age and race of the patient</td>
</tr>
<tr>
<td>BMD</td>
<td>✔</td>
<td></td>
<td>After 1-2 years of T therapy in hypogonadal men with osteoporosis or low trauma fracture consistent with regional standard of care</td>
</tr>
</tbody>
</table>


DRE = Digital Rectal Exam  
BMD = Bone Mineral Density
Guidelines for Testosterone Replacement Therapy in Hypogonadal Adult Men

Monitoring

• Refer to Urologist if
  - An increase in serum PSA >1.4 ng/mL (verified by repeat measurement) within any 12-month period of T replacement
  - Detection of prostatic abnormality on DRE
  - A PSA velocity of >0.4 ng/mL/yr using the PSA level at 6 months after initiation of T replacement as the reference
    ▪ Only applicable if PSA data are available for a period >2 years
  - AUA prostate symptom score >19

Testosterone Replacement Therapy
Contraindications and Precautions

**Contraindications**
- Male breast cancer
- Prostate cancer (known or suspected)
- Use in pregnant or breast-feeding women
- Known or suspected sensitivity to ingredients used in T delivery systems

**Precautions**
- Benign prostatic hyperplasia (BPH): especially if severe
- Can cause azoospermia
  - Testicular atrophy
- Hematocrit >50%
- Edema in patients with preexisting cardiac, renal, or hepatic disease: Do not use in uncontrolled heart failure
- ?worsening of severe obstructive sleep apnea
FDA Drug Safety Communication requiring labeling change to inform of possible increased risk of heart attack and stroke with use

- March 3, 2015: “… Health care professionals should make patients aware of the possible increased cardiovascular risk when deciding whether to start or continue a patient on testosterone therapy. ..”
The annual rate of major adverse cardiovascular event (MI, stroke death due to cardiovascular causes) was 1.7% in both groups (7 men out of 394 in each group), a rate which would be expected in an elderly population, 20% of whom had history of myocardial infarction or stroke prior to entering the study.

During a follow-up period of one year of observation after discontinuation of treatment, 2 men in testosterone group and 9 men in placebo had a cardiovascular event.

While these data are reassuring, T trials are not long enough to provide definite evidence of cardiovascular safety after testosterone therapy in elderly men.

Snyder et al, NEJM 2016

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 394)</th>
<th>Testosterone (N = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate-related event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in PSA level by ≥1.0 ng/ml</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IPSS &gt;19†</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Hemoglobin ≥17.5 g/dl</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Cardiovascular event†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction (definite or probable)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stroke (definite or probable)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction, stroke, or death from cardiovascular causes</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>78</td>
<td>68</td>
</tr>
<tr>
<td>Other‡</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
### Table 2. Change From Baseline and Estimated Differences for Primary, Secondary, and Exploratory Outcomes in the Cardiovascular Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Group</th>
<th>Estimated Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Testosterone (n = 73)</td>
<td>Placebo (n = 65)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncalcified plaque volume, mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, median (IQR)</td>
<td>204 (60 to 420)</td>
<td>317 (168 to 589)</td>
<td></td>
</tr>
<tr>
<td>Month 12, median (IQR)</td>
<td>232 (103 to 473)</td>
<td>325 (172 to 560)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline value, unadjusted mean (95% CI)</td>
<td>40 (23 to 56)</td>
<td>4 (-14 to 22)</td>
<td></td>
</tr>
<tr>
<td>LS mean (95% CI)</td>
<td>54 (12 to 97)</td>
<td>14 (-29 to 56)</td>
<td>.003</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total plaque volume, mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, median (IQR)</td>
<td>272 (84 to 600)</td>
<td>499 (246 to 925)</td>
<td></td>
</tr>
<tr>
<td>Month 12, median (IQR)</td>
<td>318 (133 to 693)</td>
<td>541 (248 to 950)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline value, unadjusted mean (95% CI)</td>
<td>57 (35 to 78)</td>
<td>21 (0 to 42)</td>
<td></td>
</tr>
<tr>
<td>LS mean (95% CI)</td>
<td>75 (22 to 128)</td>
<td>28 (-24 to 81)</td>
<td>.006</td>
</tr>
<tr>
<td>Coronary artery calcium score, Agatston units⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, median (IQR)</td>
<td>255 (43 to 963)</td>
<td>494 (146 to 1892)</td>
<td></td>
</tr>
<tr>
<td>Month 12, median (IQR)</td>
<td>244 (52 to 1013)</td>
<td>503 (146 to 2108)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline value, unadjusted mean (95% CI)</td>
<td>53 (25 to 82)</td>
<td>118 (73 to 164)</td>
<td></td>
</tr>
<tr>
<td>LS mean (95% CI)</td>
<td>64 (-19 to 146)</td>
<td>91 (7 to 174)</td>
<td>.31</td>
</tr>
</tbody>
</table>
### Low-attenuation plaque volume, mm³

<table>
<thead>
<tr>
<th></th>
<th>Baseline, median (IQR)</th>
<th>Month 12, median (IQR)</th>
<th>Change from baseline value, unadjusted mean (95% CI)</th>
<th>LS mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.1 (1.5 to 32.4)</td>
<td>15.3 (2.6 to 31.1)</td>
<td>6 (0 to 12)</td>
<td>8 (-4 to 20)</td>
</tr>
</tbody>
</table>

### Fibrous-fatty plaque volume, mm³

<table>
<thead>
<tr>
<th></th>
<th>Baseline, median (IQR)</th>
<th>Month 12, median (IQR)</th>
<th>Change from baseline value, unadjusted mean (95% CI)</th>
<th>LS mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40.0 (11.5 to 72.6)</td>
<td>43.7 (18.9 to 107)</td>
<td>9 (1 to 17)</td>
<td>12 (-7 to 30)</td>
</tr>
</tbody>
</table>

### Fibrous plaque volume, mm³

<table>
<thead>
<tr>
<th></th>
<th>Baseline, median (IQR)</th>
<th>Month 12, median (IQR)</th>
<th>Change from baseline value, unadjusted mean (95% CI)</th>
<th>LS mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>160 (51.5 to 305)</td>
<td>254 (122 to 426)</td>
<td>25 (14 to 35)</td>
<td>31 (0 to 62)</td>
</tr>
</tbody>
</table>

### Dense calcium plaque volume, mm³

<table>
<thead>
<tr>
<th></th>
<th>Baseline, median (IQR)</th>
<th>Month 12, median (IQR)</th>
<th>Change from baseline value, unadjusted mean (95% CI)</th>
<th>LS mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>69.5 (13.6 to 211)</td>
<td>173 (35.2 to 351)</td>
<td>17 (7 to 27)</td>
<td>17 (-8 to 42)</td>
</tr>
</tbody>
</table>
308 men, 60 years or older were randomized to receive testosterone gel or placebo gel daily for 3 years.

Coprimary outcomes included common carotid artery intima-media thickness and coronary artery calcium.

The small number of unadjudicated CVD events and major adverse cardiovascular events did not differ between groups:

- 3 in the testosterone vs 2 in the placebo group had myocardial infarction;
- 3 in the testosterone vs 0 in the placebo group had had a stroke,
- 1 in the testosterone group vs 0 in the placebo group had died of a cardiovascular-related event;
- 5 in the testosterone vs 2 in the placebo group had undergone coronary revascularization.
Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

Rishi Sharma¹, Olurinde A. Oni¹, Kamal Gupta², Guoqing Chen³, Mukut Sharma¹, Buddhadeb Dawn², Ram Sharma¹, Deepak Parashara²,⁴, Virginia J. Savin⁵, John A. Ambrose⁶, and Rajat S. Barua¹,⁴*  

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Received 2 June 2015; revised 1 July 2015; accepted 6 July 2015
Methodology and Patients Selection Process

117,094

Patients with total testosterone less than lower limit of reference range

1,560 patients excluded for previous history of MI, stroke before available testosterone lab result

24,522 patients excluded due to lack of baseline lab result before testosterone replacement therapy

91,012

Treated group

69,632

25,701 patients continued to have low total testosterone after treatment

43,931 patients had normal total testosterone after treatment

21,380

Untreated group

 Patients enrolled into the study

8,002 patients found to have total testosterone within normal reference range after repeat testing were excluded

13,378 untreated patients who continued to have low total testosterone
Mean duration of treatment for normalized-TRT group was 3.0±2.7 years and for non-normalized group was 1.5±1.9 years.
Testosterone Replacement Therapy and the Incidence of DVT and Pulmonary Embolism: A Retrospective Cohort Study from VA

- Normal on-Treatment sTT Group (Gp1): Adequately treated patients: 38,362.
- Low on-Treatment sTT Group (Gp2): Inadequately treated patients: 22,191.
- Untreated Subjects (Gp3): subjects with low baseline sTT but who did not receive any TRT during the study period: 10,854
- The incidence of DVT/PE was 0.5%, 0.4%, and 0.4% in Gp1, Gp2, and Gp3, respectively.

**TABLE 2**  Unadjusted and Adjusted Hazard Ratios for DVT and Pulmonary Embolism

<table>
<thead>
<tr>
<th>Model</th>
<th>Normal-on-Treatment Vs Untreated</th>
<th>Normal-on-Treatment Vs Low-on-Treatment</th>
<th>Low-on-Treatment Vs Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>Univariate</td>
<td>1.048</td>
<td>0.749-1.466</td>
<td>.7855</td>
</tr>
<tr>
<td>Multivariate</td>
<td>1.066</td>
<td>0.761-1.492</td>
<td>.7116</td>
</tr>
<tr>
<td>SIPTW</td>
<td>1.096</td>
<td>0.778-1.543</td>
<td>.5998</td>
</tr>
</tbody>
</table>
Overview of the meta-analyses

- A: cardiovascular events
- B: stroke
- C: mortality

Lancet Diabetes and Endocrinology, November 2016
FDA (March 2015): We are requiring manufacturers of approved testosterone products to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products. We are encouraging these manufacturers to work together on a clinical trial, but they are allowed to work separately if they so choose.

On the basis of the cardiovascular event rates reported in the largest systematic meta-analysis, any randomized controlled trial aiming to detect a true difference in cardiovascular risk between treatment groups receiving exogenous testosterone and their controls would require at least 17,664 participants in each trial group. (Onasanya et al, Lancet D&E, Nov 2016)

Will one randomized controlled trial resolve this issue?
SUMMARY (Androgen Use)

- FDA recommends that only “organic” hypogonadism be treated.
- TRT should be titrated to achieve serum total testosterone concentrations of ~700 in young (<40 years) men and ~400 ng/dl in elderly (>70 years) men.
- TRT can cause polycythemia and decrease sperm count.
- There is no definite evidence that TRT increases or decreases cardiovascular events.
Prior to 1980, AAS use was restricted to competitive athletes.

Public perception: only select elite athletes use AAS.

Reality: Most AAS users are not athletes. They are non-athletes who take AAS to look “good” (leaner and more muscular).

Gain muscle mass in 2 months (AAS + exercise + nutrition) rather than 12 months (exercise + nutrition).

Lifetime prevalence (cumulative incidence) of AAS use is 6%.
Prevalence of AAS, cocaine, heroin and amphetamine use among 12\textsuperscript{th} graders
Performance Enhancing drugs used by competitive athletes

Often participate in polypharmacy: erythropoietin, growth hormone, insulin, diuretics
Performance Enhancing drugs used by competitive athletes

- Competitive athletes often participate in polypharmacy: erythropoietin, growth hormone, insulin, diuretics
- Some lesser talented athletes take AAS to give them a competitive edge in high school/college sports or to qualify for the team. They do not progress far in their career due to mediocre talent and doping tests.
AAS in non-athlete weightlifters

- Median start age of AAS is 23 years.
- 3.5 million individuals in United States have used AAS.

- 30% of users (1 million) become long term users (use for many years)
Causes of AAS dependence

- Almost half of chronic AAS users have “muscle dysmorphia” disorder, an official diagnosis in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition). An insatiable desire for continuously body shaping towards, but never reaching, a desired goal.

- Treatment: cognitive behavioral therapy, SSRI, atypical antipsychotics
Causes of AAS dependence

- Cannot tolerate withdrawal
- Quick hedonic, pleasant effects: likely nongenomic, activation of reward mechanisms and overlap with opioid pathway.
Anabolic Steroids Administration

- Oral
- Injectable
- Topical-cream
- Cycling
- Stacking and pyramiding
- Dosepack
Other forms of abuse

• An even larger section of society may be taking AAS unknowingly. Many nutritional supplements that body builders take have been found to contain AAS that are not described on the label.

• AAS abusers engage in high risk behavior (unsafe sexual practices) and often start abusing cocaine and opiates (are more prone to musculoskeletal injuries).

• 70% of AAS users also meet criteria for alcohol dependence
When do they present to a physician

Current users may come to the physician because of

- side effects of AAS: erectile dysfunction, infertility or are found to have high hemoglobin concentrations
- Trying to stop AAS but going through withdrawal symptoms.
- Prolonged hypogonadism after stopping AAS.
- 56% of AAS abusers do not disclose their AAS use to any physician.
Detecting surreptitious AAS use

A combination of signs and symptoms of androgen excess as well as androgen deficiency.

- Muscular appearance
- High hemoglobin
- Low HDL
- Male pattern balding
- Acne

- Infertility, low sperm count
- Sexual dysfunction
- Gynaecomastia
- Testicular atrophy
Lab tests

- Testosterone (may be high or low depending on the drug being abused)
- Gonadotropins will be suppressed.
- While not necessary to measure, estrogen will be high unless aromatase inhibitors or non-aromatizable androgens are being used.
- Laboratories can measure known AAS in urine by mass spectrometry
- Tests by doping agencies such as testosterone: epitestosterone ratio (should be <4).
Androgenic Steroid Metabolism

- Testosterone (T) production mainly in testis
- DHT and E$_2$ mainly by peripheral conversion
- Epitestosterone - inactive T epimer
- Usual ratio of T / epiT glucuronide in urine 1:1
- Values >4:1 suspicious for doping
- Marked genetic variation: false +ve & false –ve*
- Carbon isotope ratio confirmatory testing

* JJ Schulze et al. JCEM 2008; 93: 2500-6
Side effects of AAS: cardiovascular

- Case reports of sudden cardiac death with AAS use. Normal coronaries on autopsy but hypertrophied myocardium.
- Conduction abnormalities
- Stroke or Pulmonary Embolism due to high hematocrit

- Widespread AAS abuse started in 1980s.
- Hence very few men who abused AAS long term are >50 years of age.
- Long term outcomes are not known
Side effects of AAS: cardiovascular

- Echocardiography and cardiac MRI studies show that cardiac mass is similar in bodybuilders who use or do not use AAS but myocardium contractility (lower ejection fraction, decreased diastolic function) is decreased in AAS users.

Bagghis et al, Circ Heart Fail. 2010
Side effects of AAS: Aggression

- Irritability, aggressiveness, exaggerated self confidence, reckless behavior.
- Severe symptoms are seen in a minority (idiosyncratic)
- Human studies: 109 individuals treated with androgens equivalent of 500mg of testosterone every week under blinded conditions showed a 5% prevalence of hypomania/mania in AAS vs none on placebo.
- Most AAS users take the equivalent of 1000 mg of testosterone every week.
Side effects of AAS: Infertility

- AAS abuse does not seem to cause permanent damage to spermatogenesis, even if started in teenage years.
- Recovery from transient suppression may take up to 2 years.

Sperm concentrations in 41 bodybuilders currently using anabolic steroids, 3–14 weeks ago or >14 weeks ago (upper part) and in 41 drug-free volunteers (lower part). The bars represent sperm concentrations from individual body-builders (upper panel) and from normal volunteers (lower panel). The horizontal lines indicate a concentration of 20 million/ml as lower limit of normal.
Effect of Testosterone or placebo for 24 weeks in men with T2D and HH

<table>
<thead>
<tr>
<th></th>
<th>TESTOSTERONE (n=20)</th>
<th></th>
<th>PLACEBO (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 week</td>
<td>24 weeks</td>
<td>p</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54±7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>39.0±7.8</td>
<td>38.9±8.3</td>
<td>0.66</td>
</tr>
<tr>
<td>Total testosterone (ng/dl)</td>
<td>260±87</td>
<td>562±189</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free testosterone (ng/dl)</td>
<td>4.5±1.3</td>
<td>13.1±5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calculated free testosterone (ng/dl)</td>
<td>5.6±1.1</td>
<td>15.5±6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>27±14</td>
<td>24±10</td>
<td>0.07</td>
</tr>
<tr>
<td>PSA (ng/dl)</td>
<td>0.8±0.7</td>
<td>1.0±0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Testicular size (ml)</td>
<td>18±4</td>
<td>14±4</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Side effects of AAS

- Tendon rupture: Contrary to the anabolic effects of androgens on muscle, tendons and ligaments do not hypertrophy. Ultrastructural analysis of tendons in rodents treated with anabolic steroids shows dysplasia of collagen fibrils.
- Acne: The acne is typically truncal but rarely facial, the reverse of adolescent acne.
- In adolescents, AAS abuse may prematurely close the epiphyses and stunt final height.
- Gynaecomastia, irreversible male pattern baldness.
- Hepatic adenomas, peliosis hepatis but not hepatocellular carcinoma (orally active 17-α alkylated androgens.)
AAS withdrawal syndrome

- Depressed mood, hypersomnia, anorexia
- Ethically, it is difficult to justify testosterone replacement (under physician guidance) after stopping AAS and slowly tapering the testosterone. It might prolong the recovery. There is also a potential for abuse (testosterone + AAS). Strict termination of abuse and patiently waiting for spontaneous recovery may be the best course.
- Prolonged Hypogonadism lasting over 2 years
- No trials to suggest appropriate treatment but anecdotal reports suggest that clomiphene, aromatase inhibitors, hCG may be useful.
Summary (AAS Abuse)

- AAS abuse in common in non-athletes.
- Half of the chronic AAS users have muscle dysmorphia and need psychiatric treatment.
- AAS suppresses hypothalamic pituitary gonadal axis and spermatogenesis.
- AAS abuse decreases HDL concentrations and may cause polycythemia.
- AAS abuse depresses myocardial function and may cause sudden death.
- AAS abuse should be terminated immediately by users.