Testosterone Replacement Risks & Benefits: To T or not to T?

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Learning Objectives

1. Identify key points regarding the indications for testosterone replacement therapy.
2. Describe benefits of testosterone therapy.
3. Evaluate the cardiovascular risks of exogenous testosterone.
1. Hypogonadism in Males & Testosterone Supplementation\textsuperscript{1,2,3}

A. Hypogonadism definition
   i. Decrease in one or both of the two major functions of the testes: sperm production or testosterone production

B. Causes
   i. Primary: disease of the testes
   ii. Secondary: disease of the hypothalamus or pituitary
      a. Kallmann syndrome
      b. Pituitary disorders
      c. Inflammatory diseases: sarcoidosis, histocytosis, tuberculosis
      d. HIV/AIDS
      e. Medications: opioids, hormones
      f. Obesity
      g. Stress induced

C. Pathophysiology

![Testosterone Biological Pathway](image)

**FIGURE 1: TESTOSTERONE BIOLOGICAL PATHWAY**

D. Screening
   i. Screening of testosterone deficiency is only recommended in adult men with consistent and preferably multiple signs and symptoms listed in table 1
   ii. Serum testosterone testing is suggested for the following conditions:
      a. Sellar mass, radiation to the sellar region, or other diseases of the sellar region
      b. Treatment with medications that affect testosterone production or metabolism:
         1. Glucocorticoids
         2. Opioids
c. HIV-associated weight loss
d. End-stage renal disease and maintenance hemodialysis
e. Moderate to severe chronic obstructive lung disease
f. Infertility
g. Osteoporosis or low trauma fracture, especially in a young man
h. Type 2 diabetes mellitus

Table 1: Signs and symptoms that may present in hypogonadism

<table>
<thead>
<tr>
<th>Specific signs and symptoms</th>
<th>Less specific signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduced sexual desire and activity</td>
<td>• Decreased energy, motivation, initiative, and self-confidence</td>
</tr>
<tr>
<td>• Decreased spontaneous erections</td>
<td>• Feeling sad or blue, depressed mood, dysthymia</td>
</tr>
<tr>
<td>• Breast discomfort, gynecomastia</td>
<td>• Poor concentration and memory</td>
</tr>
<tr>
<td>• Loss of body (axillary and pubic) hair, reduced shaving</td>
<td>• Sleep disturbance, increased sleepiness</td>
</tr>
<tr>
<td>• Very small (&lt;5 ml) or shrinking testes</td>
<td>• Mild anemia (normochromic, normocytic)</td>
</tr>
<tr>
<td>• Inability to father children, low or zero sperm count</td>
<td>• Reduced muscle bulk and strength</td>
</tr>
<tr>
<td>• Height loss, low trauma fracture, low bone mineral density</td>
<td>• Increased body fat, body mass index</td>
</tr>
<tr>
<td>• Hot flushes, sweats</td>
<td>• Diminished physical or work performance</td>
</tr>
</tbody>
</table>

E. Diagnosis

i. Introduction
   a. Diagnosed on the basis of persistent signs and symptoms related to androgen deficiency and assessment of consistently low testosterone levels
      1. At least on two occasions with a reliable method
   b. European guidelines recommend treatment in patients with:
      1. Decline in muscle mass and strength
      2. Reduced bone mineral density at the lumbar spine
      3. Decreased libido and erection

ii. Objective measures to determine diagnosis
   a. Both guidelines recommend obtaining two serum testosterone concentrations
      1. Taken in early morning when testosterone concentrations are highest
   b. American guideline cut off for treatment: <200 ng/dL
   c. European guideline cut off for treatment <12 nmol/L (<346 ng/dL) (Refer to Appendix A for full conversions)
      1. Recommend testing free testosterone level if between 8-12 nmol/L (230-346 ng/dL)

iii. Subjective criteria to determine diagnosis
   a. American guidelines
      1. Clinically significant symptoms of androgen deficiency
   b. European guidelines
      1. Strongest predictor was three sexual symptoms
         A. Decreased sexual thoughts
         B. Weakened morning erections
         C. Erectile dysfunction
Table 2: Diagnostic criteria for primary and secondary hypogonadism

<table>
<thead>
<tr>
<th>Primary (need all)</th>
<th>Secondary (need all)</th>
<th>Normal Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↓ Serum Testosterone</td>
<td>• ↓ Serum testosterone</td>
<td>• Total Testosterone (TT) 300-1000 ng/dL</td>
</tr>
<tr>
<td>• ↓ Sperm counts</td>
<td>• ↓ Sperm counts</td>
<td>• Sperm count &gt;15 million/mL</td>
</tr>
<tr>
<td>• ↑ Luteinizing Hormone (LH) and/or Follicle-Stimulating Hormone (FSH)</td>
<td>• Normal or ↓ LH and/or FSH</td>
<td>• LH 1.8-8.6 IU/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FSH 1.5-2.4 million IU/mL</td>
</tr>
</tbody>
</table>

iv. Clinical Features of adult-onset male hypogonadism
   a. Refer to table 1

F. Recommended Treatment Regimens
   i. Age-specific caveat of treatment:1
      a. Recommend against a general policy of offering testosterone therapy to all older men with low testosterone
      b. Suggest that clinicians consider offering testosterone therapy on an individualized basis to older men with low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency
         1. In addition to explicit discussion of the uncertainty about the risks and benefits of testosterone therapy
   ii. None are preferred over another. Refer to appendix B for a table comparing the testosterone products

   Table 3: Testosterone dosing per guideline recommendations

   **Injections**
   - Testosterone enanthate or cypionate 150-200 mg administered intramuscularly every 2 weeks or 75-100 mg weekly

   **Topical Applications**
   - Testosterone 5 mg patches, one to two applied nightly
   - Testosterone gel 5-10 g applied daily over covered areas of skin
   - Testosterone 30 mg buccal tablet applied to buccal mucosa twice daily

   iii. Contraindications against testosterone treatment
      a. Prostate cancer
      b. Prostate specific antigen (PSA) >4 ng/mL
      c. Male breast cancer
      d. Severe sleep apnea
      e. Male infertility
      f. Hematocrit >50%
      g. Severe lower urinary tract symptoms due to benign prostatic hyperplasia (BPH)

G. Goals of Treatment
   i. Restore sexual function, libido, well-being, and behavior
   ii. Produce and maintain virilization
   iii. Optimize bone density and prevent osteoporosis
   iv. Possibly normalize growth hormone levels in elderly men
v. Potentially affect the risk of cardiovascular disease
vi. Restore fertility in cases of hypogonadotropic hypogonadism
vii. Aim for total testosterone of 400-700 ng/dL

H. Testosterone product package inserts7,8,9,10,11 (see Appendix D for full table)
i. Most common side effects:
   a. ≥10% incidence: Prostate specific antigen (PSA) increase (5-11%)
      1. Transdermal application only: application site pruritus (17-37%), application site vesicles (6-12%)
   b. ≥5% incidence: Acne vulgaris (5%), headache (1-6%)
      1. Injection only: pain at injection site (5%)

I. Monitoring
i. Symptomatic response and adverse effects
   a. Every 3-6 months after treatment initiation, then annually
   b. Product specific monitoring
      1. Injectable products: Fluctuations in mood or libido, rare cough after injections
      2. Transdermal patches: Skin reaction at the application site
      3. Buccal testosterone: Alterations in taste, gum and oral mucosa irritation
      4. Transdermal gels: Administration issues such as covering the applications sites and washing 4-6 hours after application

ii. Testosterone levels
   a. 3-6 months after initiation
      1. Aim for 400-700 ng/dL
      2. Older men: aim for 400-500 ng/dL
   b. Product specific timing
      1. Injectable products: midway between injections
      2. Transdermal patches: 3-12 hours after patch application
      3. Buccal testosterone: Immediately before or after application of fresh system
      4. Transdermal gels: Any time after at least 1 week of treatment

iii. Other labs
   a. Hematocrit: if >54% stop therapy
      1. Baseline
      2. 3-6 months
      3. Annually
   b. Bone mineral density of lumbar spine and/or femoral neck
      1. 1-2 yr of testosterone therapy
         A. Hypogonadal men with osteoporosis or low trauma fracture
   c. PSA
      1. Baseline >0.6 ng/mL
         A. Digital rectal exam
         B. Recheck before initiating therapy, at 3-6 months, and then according to prostate cancer screening guidelines
B. Estimated Prevalence of Hypogonadism – results of the European Male Aging Study\textsuperscript{12}
   i. Testosterone <8.0 nmol/L = 4.1% of subjects
   ii. Testosterone <11 nmol/L = 17.0%
   iii. If testosterone < 11 nmol/L PLUS free
        testosterone <220 nmol/L PLUS at least 3
        sexual symptoms
        a. Overall prevalence of late-onset
        hypogonadism = 2.1% (63 of 2966 subjects)
        1. 0.1% for men 40 to 49 years of age
        2. 0.6% for those 50 to 59 years
        3. 3.2% for those 60 to 69 years
        4. 5.1% for those 70 to 79 years
   
C. Testosterone Utilization Trends\textsuperscript{13}
   1. 9-fold increase in testosterone replacement therapy prescriptions from 2000-2013
      A. 2013: 7.5 million prescriptions for 2.3 million individuals
      1. Men aged 45-64 years received approximately 60% of all prescriptions
      2. 20% men <45 years
      3. 20% men >65 years
      B. Median length of treatment: 3-4 months
      C. Potential reasons for increase:
         1. Approval of new products
         2. Drug sponsor promotional activities
            A. Direct-to-consumer advertising
            B. Disease-state awareness
         3. Non-pharmaceutical promotional activities such as low-T clinics
         4. Availability of professional guidelines
   2. Prescribers in 2013
      A. 20% = endocrinologists + urologists
      B. 60% = primary care providers
      C. 20% = all other specialties combined

2. Cardiovascular Risks of Low Testosterone Concentrations
   A. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic
      study. Eur J Endocrinol. 2011.\textsuperscript{14}
      i. 70 studies identified assessing the association of CVD and altered hormone levels: low testosterone and/or
         elevated 17-β-estradiol
         a. Population: No information regarding average age, specific comorbidities, or diagnosis for testosterone
            therapy is available in the published article.
         b. Inclusion criteria of studies
            1. Initial search using “testosterone, CVD, and males”
            2. Cross-sectional, longitudinal, and interventional studies included
c. Patients with CVD had significantly lower total testosterone (TT) in comparison to individuals without CVD (-2.55 [-3.39; -1.71] nmol/L) (-73.5 [-97.8, -49.3 ng/dL]) (Refer to Appendix B for comparison of testosterone levels)

d. Logistic regression model, adjusted for age and body mass index (BMI), was performed to confirm association of low testosterone and CVD
   1. HR = 0.837 [0.823-0.852] for each nmol/L (29 ng/dL) increment of testosterone (P<0.0001)

B. Systemic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. *Andrology*, 2014.\textsuperscript{15}

i. 18 studies identified assessing the association between testosterone and cardiovascular disease (CVD) mortality

a. Population
   1. Testosterone cut-offs ranged from <200 ng/dL to <400 ng/dL
   2. Included populations
      A. General population
      B. Without prior stroke or trans ischemic attack (TIA)
      C. With chronic heart failure (CHF)
      D. With myocardial infarction (MI)
      E. Referred for coronary angiography
      F. End stage renal disease (ESRD) with or without hemodialysis
      G. Presenting to erectile dysfunction clinic
      H. Metabolic syndrome
      I. Type 2 diabetes mellitus with or without coronary artery disease

b. 14 studies demonstrated that low testosterone was significantly associated with increased CVD mortality (See Appendix C for details of the studies)\textsuperscript{3}

c. From those studies, the following diseases were associated with low testosterone:
   1. coronary heart disease
   2. hypertension
   3. stroke
   4. peripheral artery disease

3. Risks Associated with Exogenous Testosterone Therapy

A. Hypogonadism treatment guidelines and medical literature review

i. Breast cancer
   a. Long term use (>10 years) of parenteral testosterone for male hypogonadism may increase risk

ii. Polycythemia
   a. May increase hematocrit requiring dose adjustment or discontinuation. Discontinue therapy if hematocrit exceeds 54%; may reinitiate at lower dose.\textsuperscript{1,16}

iii. Prostate cancer
   a. May increase the risk of prostate cancer. Withhold therapy pending urological evaluation in patients with palpable prostate nodule or induration, PSA >4 ng/mL, or PSA >3 ng/mL in men at high risk of prostate cancer.\textsuperscript{1}
iv. Diseases exacerbated by fluid retention
   a. Use with caution in patients with diseases that may be exacerbated by fluid retention, including cardiac, hepatic, or renal dysfunction; testosterone may cause fluid retention. Treatment of androgen deficiency syndromes is not recommended for men with uncontrolled or poorly controlled heart failure.¹

B. FDA Warning:
   “Based on our findings, we are requiring labeling changes for all prescription testosterone products to reflect the possible increased risk of heart attacks and strokes associated with testosterone use. Health care professionals should make patients aware of this possible risk when deciding whether to start or continue a patient on testosterone therapy. We are also 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.”¹⁷

   i. Major Concerns from the Experts Present on the FDA Committee:
      a. Benefit not established in age-related hypogonadism
         1. Predominant use of testosterone in the United States is for this condition in men aged 40-64 years
      b. No studies completed in patients who report symptoms of low testosterone but have normal testosterone levels. This set of patients may be incorrectly diagnosed¹⁸

4. Clinical Question

   For patients without clinically diagnosed primary or secondary hypogonadism does exogenous testosterone therapy increase the risk of cardiovascular disease and/or mortality?

5. Literature Review

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Purpose</strong></td>
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<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
</tr>
</tbody>
</table>
Outcomes
- Primary outcome: change from baseline in maximal voluntary muscle strength in a leg-press exercise
- Secondary outcomes included changes from baseline
  - chest-press strength
  - 50-m walking speed
  - stair-climbing speed and power
  - lift-and-lower test

Methods
Randomized to receive either placebo or testosterone gel applied daily for 6 months

Statistics
- Study designed to have 90% power to detect a 25 kg increase in bilateral leg strength in 252 men
- Proportion of subjects in each group with adverse events compared with chi-square and Fisher’s exact tests
  - Odd ratios were calculated with logistic regression
  - Time to report of first adverse event or censoring was compared with Kaplan-Meier and Cox proportional-hazards models

Results
- 209 men were enrolled and randomized at the time of the adverse event analysis
  - 129 had completed the 6-month intervention period
    - 47 received the study medication for at least 12 weeks
  - 23 versus 5 in the testosterone and placebo group had a cardiovascular adverse event (Refer to Tables 5a and 5b)
- Baseline comorbidities (testosterone %, placebo %). Significant differences in bold
  - Preexisting CVD (53, 47)
  - Obesity (45, 49)
  - Controlled hypertension (85, 78)
    - Antihypertensive therapy (85, 73; p=0.04)
  - Diabetes mellitus (24, 27)
    - Avg A1c (6.2±0.7, 6.1±0.7)
  - Hyperlipidemia (63, 50; p=0.05)
    - Statin therapy (62, 47; p=0.03)

### Table 4a Risk of Adverse Events with Testosterone Therapy, According to Category*

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Total Risk Odds Ratio (95% CI)</th>
<th>Instantaneous Risk Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted adjusted</td>
<td>unadjusted adjusted</td>
</tr>
<tr>
<td>MedDRA cardiac</td>
<td>10.6 (1.3-84.5)</td>
<td>10.5 (1.3-82.4)</td>
</tr>
<tr>
<td>Atherosclerosis-related</td>
<td>7.2 (0.9-59.7)</td>
<td>7.1 (0.9-57.8)</td>
</tr>
<tr>
<td>Cardiovascular-related</td>
<td>5.4 (2.0-14.9)</td>
<td>5.0 (1.9-13.2)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>2.6 (1.1-6.2)</td>
<td>2.6 (1.1-5.9)</td>
</tr>
<tr>
<td>Necessitating referral for medical</td>
<td>2.3 (0.98-5.3)</td>
<td>2.3 (1.1-5.2)</td>
</tr>
<tr>
<td>evaluation</td>
<td>5.2 (1.8-14.6)</td>
<td>5.2 (2.0-13.5)</td>
</tr>
</tbody>
</table>

*MedDRA is the adverse event classification dictionary endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

*Total risk refers to the risk of an adverse event occurring over the entire study period after randomization (24 week treatment + 12 week observation phase). Instantaneous risk refers to the risk of an adverse event occurring at any specific time. Unadjusted odds and hazard ratios were estimated with the use of simple logistic regression. Adjusted odds and hazard ratios were estimated with the use of multiple logistic regression with adjustment for age group; body-mass index; presence or absence of diabetes, hypertension, hyperlipidemia; and high-density lipoprotein cholesterol level.

*Adjusted estimates are not applicable (NA) because there was only one event in the placebo group.

*Includes myocardial infarction, sudden death, angioplasty, coronary-artery bypass grafting, and stroke.
### Table 4b Events that occurred in the testosterone and placebo group

<table>
<thead>
<tr>
<th>Testosterone (n=1 unless otherwise noted)</th>
<th>Placebo (n=1 for all events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Abnormalities present on ECG (n=4)</td>
<td>o Arrhythmia and carotid bruit</td>
</tr>
<tr>
<td>o Acute coronary syndrome</td>
<td>o Carotid-artery plaque identified on ultrasound</td>
</tr>
<tr>
<td>o Atrial fibrillation with RVR plus CHF exacerbation resulting in hospitalization</td>
<td>o Elevated blood pressure</td>
</tr>
<tr>
<td>o Chest pain (n=2)</td>
<td>o Syncope</td>
</tr>
<tr>
<td>o Coronary-artery bypass grafting (CABG)</td>
<td>o Tachycardia</td>
</tr>
<tr>
<td>o Elevated blood pressure (n=3)</td>
<td></td>
</tr>
<tr>
<td>o Myocardial infarction (n=3)</td>
<td></td>
</tr>
<tr>
<td>▪ One resulted in death</td>
<td></td>
</tr>
<tr>
<td>o Peripheral edema (n=4)</td>
<td></td>
</tr>
<tr>
<td>o Stroke</td>
<td></td>
</tr>
<tr>
<td>o Syncope (n=2)</td>
<td></td>
</tr>
<tr>
<td>o Tachycardia with fatigue</td>
<td></td>
</tr>
</tbody>
</table>

### Author’s Conclusions

- Trial was stopped before enrollment was completed due to higher incidence of adverse cardiovascular events in the testosterone group than in the placebo group
- Caution is warranted in interpreting this finding based on
  - Small numbers of events
  - Limitations with respect to the ascertainment of adverse events
  - Unknown ability to extrapolate to other doses and formulations of testosterone
  - Unknown ability to extrapolate other populations
    - Young men who have hypogonadism without cardiovascular disease or limitations in mobility

### Comments

- **Strengths:**
  - Study population not limited to patients with primary or secondary hypogonadism
    - Included men who have lower testosterone that may be due to normal aging progression
- **Limitations:**
  - Study was not powered to detect a difference in cardiovascular events
    - Not the main aim of the study
  - Study was not completed and had to be discontinued prematurely due to the adverse events
  - Relatively healthy elderly study population
    - Pertinent comorbidities were controlled or treated prior to study enrollment
- **Application:**
  - Prior studies had not shown or revealed additional cardiac risk
    - Challenges CVD benefit assumption
  - Incidental findings of cardiovascular events during treatment with testosterone prompts additional investigation with studies intended to detect CVD events

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<table>
<thead>
<tr>
<th>Purpose</th>
<th>Assess the association between testosterone treatment and mortality in men with low testosterone levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Observational, retrospective cohort study from 7 VA medical centers for patients from January 1, 2001 through December 31, 2005</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Veterans, over the age of 40 years, with a low total testosterone (≤ 250 ng/dL) between January 1, 2001 and December 31, 2002</td>
</tr>
</tbody>
</table>
| Exclusion | o History of prostate cancer  
  o Previous treatment with testosterone or antiandrogens |
Outcomes
- Primary outcome: Total mortality to end of follow up (December 31, 2005)
  - Ascertained by VA BIRLS (Beneficiary Identification Records Locator Subsystem)-Death File and the Social Security Administration-Death Master File which is in accordance with the National Death Index greater than 95% of the time

Methods
- Cohort of men in the VA with total testosterone <250 ng/dL
- Testosterone therapy determined from pharmacy prescriptions including date of refills
  - Classified as having stopped testosterone treatment 90 days after final refill of testosterone was finished
  - System was unable to associate prescriptions with specific indication

Statistics
- Time-to-event models to describe the relationship between testosterone treatment initiation and risk of death
- Kaplan-Meier survival curves were used to illustrate unadjusted survival times for the testosterone-treated and untreated men
- Hazard ratios and 95% confidence intervals for mortality risk were calculated to compare testosterone-treated and untreated men
  - Cox regression models were adjusted for age, site, baseline testosterone level, BMI, overall medical morbidity, hospitalization in the past year, diabetes mellitus, and coronary heart disease
  - Sensitivity analysis which excluded men who died within the first year of follow-up to minimize the potential bias for nontreatment in the most seriously ill men

Results
- 1031 men were included in the study after exclusion criteria were applied
  - 633 patients went untreated
  - 398 patients had testosterone therapy
- Observed decrease in the hazard ratio for all-cause mortality in patients who were treated with testosterone therapy (Refer to Table 6a)

Table 5a: Mortality in testosterone-treated and -untreated men

<table>
<thead>
<tr>
<th>Testosterone exposure group</th>
<th>Person-years</th>
<th>Deaths</th>
<th>Mortality per 100 person-years</th>
<th>Fully adjusted HR (95% CI)</th>
<th>Sensitivity HR (95% CI)</th>
<th>Propensity score HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated (n=633)</td>
<td>2290</td>
<td>131</td>
<td>5.73</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Treated (n=398)</td>
<td>1190</td>
<td>41</td>
<td>3.44</td>
<td>0.61 (0.42-0.88)</td>
<td>0.47 (0.29-0.76)</td>
<td>0.64 (0.44-0.95)</td>
</tr>
<tr>
<td>Total (n=1031)</td>
<td>3480</td>
<td>172</td>
<td>4.95</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Author's Conclusions
- Testosterone treatment was associated with decreased mortality in an observational cohort of middle-aged male veterans with low total testosterone levels and high chronic medical morbidity.
  - Due to limitations, these results should be viewed cautiously and cannot be interpreted as showing beneficial effects of testosterone treatment or as establishing a causal relationship between testosterone treatment and reduced mortality.
  - Results do provide impetus for conducting a large-scale, double-blind, placebo-controlled clinical trial to better understand the effect of testosterone treatment on the health of older men

Comments
- Strengths:
  - High amount of patients with multiple comorbidities, more generalizable to older men who may be more susceptible to adverse effects of testosterone therapy
- Limitations:
  - Specifically excluded patients who were treated with testosterone but had normal testosterone levels
- No assessment of symptomatic improvement
- Statistical analysis did not account for the time variance between patients depending on when they entered the study or started testosterone
- Did not assess for cardiovascular disease related deaths specifically
- Confounding bias that men who go untreated for hypogonadism are likely sicker than men of normal testosterone
  - Gives more strength to supplement low testosterone than to say that it is safe when compared to men who have normal testosterone
  - No comparison to men with normal testosterone
- Application
  - In patients with directly observed low testosterone there may be mortality benefit in providing testosterone supplementation over going untreated
  - Casts doubt on theory of increased mortality risk with testosterone replacement
- Still unknown if patients were clinically indicated for testosterone therapy
  - Doesn’t assess CVD deaths - cannot extrapolate testosterone benefit in CVD


<table>
<thead>
<tr>
<th>Purpose</th>
<th>Assess the association between testosterone therapy and all-cause mortality, MI, or stroke and determine if this is modified by underlying coronary artery disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Retrospective chart review of the described patient population until an outcome event or the end of follow-up (January 23, 2012)</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Veterans who started testosterone therapy, with a total testosterone &lt;300 ng/dL, after having a coronary angiography between 2005 and 2011</td>
</tr>
</tbody>
</table>
| Exclusion | • No previous coronary angiography  
• No baseline testosterone level prior to initiating therapy  
• Prescribed testosterone after MI  
• Hematocrit >50%  
• Prostate specific antigen (PSA) ≥ 4.0 ng/mL |
| Outcomes | Primary outcome:  
  - Composite end point of time to all-cause mortality or to hospitalization for MI or ischemic stroke  
    - All-cause mortality assessed via the VA vital status file which has good agreement with the National Death Index  
    - MI and stroke were assessed via ICD-9 codes from VA inpatient treatment files |
| Methods | • Total testosterone levels were obtained from VA laboratory files  
  - Level closest in timing to the procedure date was included in analysis  
• Coronary artery disease was present if there was 20% or more stenosis in any epicardial vessel as recorded in CART by the physician performing the procedure  
  - No evidence of CAD was defined as less than 20% stenosis in all epicardial vessels on angiography  
    - Based on standardized definitions of flow-limiting stenosis. |
| Statistics | • Employed stabilized inverse probability of treatment weighting to adjust for any unmeasured confounders  
  - Variables included demographics, comorbidities, and procedures  
• Testosterone therapy treated as a time-varying covariate  
  - Cox proportional hazards models with stabilized inverse probability of treatment weighting were used to assess the association between testosterone therapy and the primary outcome |
| Results | • Cohort of 8709 veterans were included in the study  
  - 20% had a history of MI  
  - 50% had diabetes  
  - >80% had CAD |
- 7486 patients did not receive testosterone therapy
- 1223 patients received testosterone
- No statistical difference in absolute risk 1, 2, and 3 years post coronary angiography
- Adjusted Kaplan-Meier survival curves demonstrated a significant difference
  - Refer to Figure 3 for the curves, hazard ratio, and 95% CI
- No significant difference of the effect of testosterone on patients with or without CAD
- No significant difference in adverse outcomes between the various testosterone preparations used
  - Gel, injections, patches

**Author’s Conclusions**
- Use of testosterone therapy with significant medical comorbidities was associated with increased risk of mortality, MI, or ischemic stroke
  - These findings were not modified by the presence of CAD

**Comments**
- **Strengths:**
  - Objective measure of cardiovascular disease and clinical outcomes
  - Used various testosterone products
  - Large presence of comorbidities
- **Limitations:**
  - Limited number of patients who had extended follow up
    - 267 patients at 2000 days post coronary angiography
  - Retrospective review limited by refill history and ICD-9 codes rather than chart review
  - Limited to the VA system population
- **Application:**
  - Evidence supports concern for increased risks of testosterone supplementation in less healthy populations


<table>
<thead>
<tr>
<th>Purpose</th>
<th>Assess the effect of testosterone therapy on risk of acute non-fatal myocardial infarction in younger men who may or may not have pre-existing cardiac disease</th>
</tr>
</thead>
</table>
| Design | Retrospective cohort using the Truven Health MarketScan® Commercial Claims and Encounters Database
  - Data set included: demographics (year of birth, gender), diagnoses, procedures, and prescriptions
    - No data regarding indications for testosterone therapy prescriptions, race, laboratory findings, occupational, environmental, or lifestyle factors |
| Inclusion | Men who filled their first prescription of testosterone therapy, not containing estrogen, during the period of 2006-2010 compared with men who filled their first prescription for a phosphodiesterase type 5 inhibitor during that same period |
| Exclusion | History of an MI prior to first prescription |
| Outcomes | Primary outcome: diagnosis of acute MI within 90 days of first fill of a prescription (testosterone or PDE5i)
  - Post-prescription follow-up ranged from 91 to 180 days |
Methods

- Included men had a minimum of 22 months of continuous enrollment for analyses with post-prescription follow-up intervals of 90 days
- Comparison population was men who filled a first prescription for phosphodiesterase type 5 inhibitors between January 1, 2008 and September 30, 2010
  - Some indications for prescription were similar to those for TT prescription.
  - Commonly prescribed to older men, does not have androgenic effects, and is not metabolized to other sex steroid hormones, such as dihydrotestosterone or estrogens
- No data was available on how much of the prescribed medication was consumed
  - The most common TT prescriptions were testosterone gel, testosterone micronized, testosterone cypionate, and testosterone transdermal system.
- Pre-prescription interval was the one year prior to the initial prescription
- Post-prescription interval was 90 days following the initial prescription,
  - Patients were followed until a diagnosis of acute non-fatal myocardial infarction, refilled first prescription, or 90 days following initial prescription, whichever occurred first

Statistics

- Poisson regression model for the MI rate to obtain doubly robust estimates of effect of population differences between the two prescription groups
- Estimated the ratio of rate ratios (RRR)
  - Numerator of the RRR is the rate ratio for TT prescription relative to PDE5I in the post-prescription interval
  - Denominator is the rate ratio for TT prescription relative to the PDE5I in the pre-prescription interval
  - From a Poisson regression model with MI as the outcome, log-exposure time as an offset

Results

- 222,872 patients included in the cohort analysis
  - Testosterone group n=55,593
    - Also grouped by age over or under 65 years
  - PDE5I group n=167,279

<table>
<thead>
<tr>
<th>TESTOSTERONE THERAPY</th>
<th>All Ages</th>
<th>Age &lt;65 years</th>
<th>Age ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>55,593</td>
<td>48,539</td>
<td>7,054</td>
</tr>
<tr>
<td>Pre-prescription</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>193</td>
<td>156</td>
<td>37</td>
</tr>
<tr>
<td>Rate per 1,000 PY (95% CI)</td>
<td>3.48 (3.02, 4.01)</td>
<td>3.22 (2.75, 3.77)</td>
<td>5.27 (3.81, 7.27)</td>
</tr>
<tr>
<td>Post-prescription</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>65</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Rate per 1,000 PY (95% CI)</td>
<td>4.75 (3.72, 6.05)</td>
<td>3.76 (2.81, 5.04)</td>
<td>11.52 (7.43, 17.86)</td>
</tr>
<tr>
<td>Rate Ratio (post/pre) (95% CI)</td>
<td>1.36 (1.03, 1.81)</td>
<td>1.17 (0.84, 1.63)</td>
<td>2.19 (1.27, 3.77)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PDE5I THERAPY</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>167,279</td>
<td>141,512</td>
<td>25,767</td>
</tr>
<tr>
<td>Pre-prescription</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>695</td>
<td>556</td>
<td>139</td>
</tr>
<tr>
<td>Rate per 1,000 PY (95% CI)</td>
<td>3.48 (3.02, 4.01)</td>
<td>3.22 (2.75, 3.77)</td>
<td>5.27 (3.81, 7.27)</td>
</tr>
<tr>
<td>Post-prescription</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>152</td>
<td>119</td>
<td>33</td>
</tr>
<tr>
<td>Rate per 1,000 PY (95% CI)</td>
<td>3.75 (3.19, 4.40)</td>
<td>3.42 (2.76, 4.24)</td>
<td>6.06 (4.26, 8.63)</td>
</tr>
<tr>
<td>Rate Ratio (post/pre) (95% CI)</td>
<td>1.08 (0.93, 1.24)</td>
<td>1.06 (0.91, 1.24)</td>
<td>1.15 (0.83, 1.59)</td>
</tr>
</tbody>
</table>

| RRR¥             |          |               |               |
| With history of heart disease | 2.07 (1.05, 4.11) | 1.90 (0.66-5.50) |
| Without history of heart disease | 0.91 (0.60, 1.37) | 2.41 (1.12, 5.17) |

¥RRR = adjusted ratio of the rate ratios (comparing RR of Testosterone versus PDE5I)
*pre-prescription is 1 year interval prior to first prescription
Author’s Conclusions

- Among men aged 65 years and older, observed a two-fold increase in the risk of MI in the 90 days after filling an initial TT prescription
  - Risk declined to baseline in the 91 to 180 days after initial TT prescription, among those who did not refill their prescription
- Among younger men with a history of heart disease, observed a two to three-fold increased risk of MI in the 90 days following an initial TT prescription and
  - Equal risk in younger men without such a history
- Among older men, the two-fold increased risk was associated with TT prescription regardless of cardiovascular disease history
  - Analysis was based on relatively small numbers of MI cases in each subgroup

Comments

- Strengths
  - Included patients regardless of testosterone levels and indications
    - Reflecting real-world prescribing population
  - Assessed patients within the median length of treatment
- Limitations
  - No testosterone level testing data available
  - Focus only non-fatal MI
  - Limited to events occurring within the first 90 days
  - Retrospective nature based on ICD-9 codes and refill history
- Application
  - In the general population of patients prescribed testosterone therapy the risk of MI is increased; however, the overall incidence is still low
  - Only study that includes patients who may only be symptomatic without having low testosterone

6. Future Direction

A. Anticipated Literature per FDA mandate to provide greater clarity?

Table 8: Randomized, placebo-controlled, double-blind study of five coordinated testosterone treatment trials in older men, also known as “The T-Trial”

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Test the hypotheses that testosterone treatment of elderly men will result in more favorable changes in symptoms (physical or sexual function, vitality, cognition, and anemia) than those in the placebo arm</th>
</tr>
</thead>
</table>
| Design  | Multi-center placebo controlled trial in 12 clinical sites across the United States of men 65 years and older with testosterone < 300 ng/dL
- The Cardiovascular Trial:
  - To evaluate if testosterone therapy results in more favorable changes in cardiovascular risk factors when compared to placebo
- The Bone Trial:
  - To evaluate if testosterone therapy results in an increase in volumetric trabecular bone mineral density of the lumbar spine when compared to placebo
- Pharmacokinetic Study
  - To examine the variability of the serum testosterone concentrations after application of testosterone gel or placebo
  - AndroGel® (testosterone gel)
| Outcomes | Primary objectives:
- Increase from baseline of ≥50 m in 6 minute walk test
- Change from baseline in non-calcified plaque volume measured by CT angiography
- Increase in hemoglobin by ≥ 1 g/dL in men with anemia of unknown cause at baseline |
| Comments | Pertinent Timeline
- Start: November 2009
  - Estimated enrollment: 800 |
7. Conclusion

A. Clear benefit of testosterone therapy has been established in males with hypogonadism
   a. There is currently little to no evidence regarding benefit in males with symptoms of low T with normal testosterone levels.
   b. Current literature uses patients who don’t necessarily meet diagnostic criteria for hypogonadism

B. Growing preponderance of literature suggests at least marginal increase in risk of cardiovascular risk of testosterone therapy when compared with a cohort population.

C. Lack of efficacy data and increasing data showing increased CVD risk prompts clinicians to limit prescribing testosterone therapy to patient populations in whom significant clinical improvement has been demonstrated.
   a. Would recommend treatment in hypogonadism as defined in the European practice guidelines
      i. Additional caution would be given to individuals over 65 years of age with significant comorbidities such as diabetes or obesity
   b. Would not recommend treatment in patients who only have symptoms of low T
   c. Would not recommend treatment in patients with a history of CVD
### Appendix A

**Conversion of testosterone levels**

<table>
<thead>
<tr>
<th>Total Testosterone ng/dL</th>
<th>Total Testosterone nmol/L</th>
<th>Bioavailable Testosterone ng/dL</th>
<th>Bioavailable Testosterone nmol/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>&lt;3.4</td>
<td>20-29 years: 83-257</td>
<td>2.9-8.9</td>
</tr>
<tr>
<td>100-200</td>
<td>3.5-6.9</td>
<td>30-39 years: 72-235</td>
<td>2.5-8.1</td>
</tr>
<tr>
<td>201-300</td>
<td>7-10.4</td>
<td>40-49 years: 61-213</td>
<td>2.1-7.4</td>
</tr>
<tr>
<td>&gt;300 (normal)</td>
<td>&gt;10.5</td>
<td>50-59 years: 50-190</td>
<td>1.7-6.6</td>
</tr>
<tr>
<td>Free Testosterone ng/dL</td>
<td>Free Testosterone nmol/L</td>
<td>60-69 years: 40-168</td>
<td>1.4-5.8</td>
</tr>
<tr>
<td>&lt;9</td>
<td>&lt;31.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-30 (normal)</td>
<td>31.3-104</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Appendix B

**Comparison of Testosterone Products**

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Agent</th>
<th>Availability</th>
<th>Dosing</th>
<th>Advantages/Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral preparations</td>
<td>Fluoxymesterone (Androxy)</td>
<td>10 mg tablets</td>
<td>5-20 mg once daily</td>
<td>Advantages: Self-administration, dosing flexibility, immediate discontinuation.</td>
</tr>
<tr>
<td></td>
<td>Methyltestosterone (Android, Methitest, Testred)</td>
<td>Androxy, Testred: 10 mg capsules Methitest: 10 mg tablets</td>
<td>10-50 mg once daily</td>
<td>Disadvantages: Variable response. Adverse lipid changes. Not recommended for treating androgen deficiency due to higher potential for hepatoxocity</td>
</tr>
<tr>
<td>Long-acting parenteral preparations</td>
<td>Testosterone cypionate (Depot-testosterone, generics)</td>
<td>100 mg/mL, 200 mg/mL injection</td>
<td>Cypionate/Enanthate 50-400 mg IM every 2-4 weeks</td>
<td>Advantages: Inexpensive, short acting preparation that allows drug withdrawal in case of onset of side effects Disadvantages: Frequent IM injections. Fluctuations in testosterone levels. Injection site pain. Excessive erythrocytosis.</td>
</tr>
<tr>
<td></td>
<td>Testosterone enanthate (Delatestryl, generics)</td>
<td>200 mg/mL injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal Patch</td>
<td>Androderm</td>
<td>2 or 4 mg/day</td>
<td>4 mg/day patch applied to back, abdomen, upper arms, or thighs at night</td>
<td>Advantages: Convenient to use. Mimics normal diurnal testosterone changes. Disadvantages: skin reactions in over a third of patients</td>
</tr>
<tr>
<td>Transdermal gels and solution</td>
<td>Androgel</td>
<td>1% gel</td>
<td>5 g (50 mg of testosterone) once daily applied to shoulders, upper arms, or abdomen. Increase to 75 mg and then 100 mg if needed.</td>
<td>Advantages: Less skin irritation than patches. Provides normal testosterone levels without much fluctuation. Disadvantages: Transfer of gel or solution from one person to another.</td>
</tr>
<tr>
<td></td>
<td>Androgel 1.62%</td>
<td>1.62% gel</td>
<td>Start with 40.5 mg of testosterone (2 pump actuations) applied once daily in the morning to shoulders and upper arms. Max dose is 81 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fortesta</td>
<td>2% gel</td>
<td>Start with 40 mg (4 pump actuations) once daily in the morning applied to thighs. Max dose is 70 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testim</td>
<td>1% gel</td>
<td>5 g (50 mg of testosterone) once daily applied to shoulders or upper arms. Increase to 100 mg if needed.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Axiron</td>
<td>2% solution</td>
<td>Start with 60 mg (2 pump actuations, 1 applied to each underarm) each morning. Increase to 90-120 mg if needed.</td>
<td></td>
</tr>
<tr>
<td>Buccal System</td>
<td>Striant</td>
<td>30 mg buccal system</td>
<td>Apply one buccal tablet to gum area above incisor tooth every 12 hours, alternating side with each application.</td>
<td>Advantages: Provides therapeutic testosterone levels without large fluctuations. Disadvantages: May cause mouth and gum irritation, or taste alteration.</td>
</tr>
</tbody>
</table>
## Appendix C

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Follow-up</th>
<th>N</th>
<th>Patient Studied</th>
<th>Results</th>
</tr>
</thead>
</table>
| Khaw 2007     | Norway  | 7 years   | 2314| Population based | Mortality, OR Quintile 2,3,4 vs. 1 OR for mortality for increasing quartiles of endogenous testosterone compared with the lowest quartile  
**CVD**  
0.89 (0.60-1.32)  
0.62 (0.39-0.92)  
0.53 (0.32-0.86)  
**Coronary Heart Disease**  
0.71 (0.43-1.17)  
0.59 (0.39-1.00)  
0.52 (0.28-0.97) |
| Laughlin 2008 | USA     | 11.8 years| 794 | Population based | Mortality, HR (95% CI) lowest quartile used as reference  
**CVD**  
1.38 (1.02-1.85) |
| Yeap 2009     | Australia | 3.5 years | 3443| Males without prior stroke or TIA | Survival – lowest quartile used as reference  
Stroke & TIA-free survival (Kaplan Meier)  
Stroke: p =0.014  
TIA: p=0.01  
Incident stroke or TIA  
HR: 1.99 (1.33-2.99) |
| Haring 2011   | Germany | 9.9 years | 1822| Males with CKD, albuminuria, kidney dysfunction | Mortality, HR – age specific 10th percentile used as reference  
**CVD** in patients with kidney dysfunction  
2.01 (1.21-3.34) |
| Hyde 2012     | Australia | 5.1 years | 4249| Population based | Mortality, HR – free testosterone 100 vs 280 pmol/L  
**CVD**  
1.71 (1.12-2.62) |
| Malkin 2010   | UK      | 6.9 years | 930 | Males with coronary disease undergoing coronary angiography | Mortality, HR (95% CI)  
Vascular  
TT <15.1 nmol/L: 1.86 (1.1-3.2)  
TT <8.1 nmol/L: 1.6 (0.95-2.85) |
| Lerchbaum 2012| Austria | 7.7 years | 2069| Males referred for coronary angiography | Mortality, HR (95% CI) – free testosterone <22 nmol/L  
**CVD**  
1.77 (1.23-2.55) |
| Corona 2010   | Italy   | 4.3 years | 1687| Males presenting to ED clinic | Mortality, HR (95% CI) – total testosterone <230 ng/dL and 230-<300 ng/dL  
**CVD**  
TT <230: 12.2 (1.9-79.5)  
TT 230-<300: 5.9 (1.6-21.7) |
| Carrero 2010  | Sweden  | 41 months | 126 | Male patients with ESRD, on HD | Mortality, HR (95% CI) – T <33rd percentile  
All cause  
1.03 (1.24-3.31)  
**CVD**  
3.19 (1.49-6.83) |
| Kyriazis 2011 | Greece  | 37 months | 111 | Male HD patients | Mortality, HR (95% CI) – TT <8 nmol/L  
**CVD**  
2.92 (1.08-7.87) |
| Yilmaz 2011   | Turkey  | 31 months | 239 | Males with CKD | Fatal and non-fatal CV events, HR – TT <10 nmol/L  
TT: every nmol/L increase in TT reduced the risk of suffering CV even during follow-up by 22% |
| Ponikowska 2010| Poland | 19 months | 153 | Males with T2DM and stable CAD | Mortality, HR (95% CI) - TT <10th percentile of healthy peers  
**CVD**  
0.58 (0.39-0.87) |
# Appendix D

<table>
<thead>
<tr>
<th>Organ Class</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia, hematocrit or hemoglobin increased</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Tachycardia, atrial fibrillation, pulmonary embolism, and deep vein thrombosis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Inflammation and pain at the site of intramuscular injection. Edema, malaise, fatigue, application site burning, contact dermatitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Cholestatic jaundice, alterations in liver function tests, hepatocellular neoplasms and peliosis hepatitis</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity, including skin manifestations and anaphylactoid reactions</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Increased appetite, urine calcium decrease, glucose tolerance impaired, elevated cholesterol, retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia, insomnia, headache, dizziness</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Personality disorder, confusion, anger, aggression, cognitive disturbance, abuse, emotional lability</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Gynecomastia, excessive frequency and duration of penile erections, and oligospermia. Prostate carcinoma, enlarged prostate (benign), free prostate-specific antigen increased, testicular atrophy, epididymitis, priapism, impotence, precocious puberty, mastodynia</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Hirsutism, male pattern of baldness, seborrhea, and acne</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>
REFERENCES


13. FDA Transcript of Dr. Rita Jain’s testimony during the joint meeting of Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) conducted on September 17, 2014. p128-139.


18. FDA Transcript of Dr. Peter Snyder and Dr. Mark Sigman’s testimony during the joint meeting of Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) conducted on September 17, 2014. p36-73.


