Hypogonadism in Men

A Best Practice Approach

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Orlando Heath
A large study has found substantial risks in prescribing testosterone to middle-age and older men for a variety of ailments. One part of the study found that testosterone doubled the risk of cardiovascular disease in more than 7,000 men who were 65 years old or older, essentially confirming findings in previous studies. The other part found that testosterone almost tripled the risk of heart attacks in a group of more than 48,000 middle-age men with previous histories of heart disease. The harm in both cases occurred within 90 days of receiving the prescription.
“Many American men have embarked on a perilous course of overtreatment”

“Testosterone is now being prescribed to men who are simply reluctant to accept the fact that they are getting older”

“Drug companies have shamelessly pushed the notion”

“Dangers of seeking a quick fix for aging”
Utilize lab testing in appropriate patients who have complaints consistent with the often subtle signs and symptoms of hypogonadism.

Select testosterone replacement therapy based on patient preference and safety in patients with hypogonadism.

Monitor the effectiveness and side effects of testosterone replacement therapy in your patients being treated for hypogonadism with testosterone replacement therapy.
How is Hypogonadism Defined by Endocrine Society?

A clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa caused by the disruption of one or more levels of the hypothalamic-pituitary-testicular (HPT) axis

Why Do We Need Testosterone?
The Myth of Testosterone
The Reality of Testosterone

<table>
<thead>
<tr>
<th>Physiological Effects of Testosterone in Male Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintains reproductive tissues</td>
</tr>
<tr>
<td>Stimulates spermatogenesis</td>
</tr>
<tr>
<td>Stimulates and maintains sexual function</td>
</tr>
<tr>
<td>Increases body weight and nitrogen retention</td>
</tr>
<tr>
<td>Increases lean body mass</td>
</tr>
<tr>
<td>Maintains bone mass</td>
</tr>
<tr>
<td>Promotes sebum production, and axillary and body hair growth</td>
</tr>
<tr>
<td>Stimulates erythropoiesis</td>
</tr>
</tbody>
</table>

Hypogonadism Is Underdiagnosed and Undertreated

Baltimore Longitudinal Study on Aging\(^1\)

- Low testosterone in 19% of men 60 years and older

Hypogonadism in Males Study\(^2\)

- Low testosterone in 39% of men 45 years and older

Boston Area Community Health Survey\(^3\)

- 24% of men age 39-79 years had biochemical hypogonadism

Only 5%-35% of hypogonadal males actually receive treatment\(^4,5\)

- 5.6% of men were symptomatic

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Prevalence of Low Testosterone (<300 ng/dL) Increases with Age

The Dilemma Is That Low Testosterone Levels Are Associated with an Increased Mortality

VA Puget Sound 8-year study of 858 men

Low T <250 ng/dL or a free T <0.75 ng/dL

All-cause mortality was 34.9% in men with low T and 20.1% in men with normal T

Improved Survival in Men with Coronary Heart Disease

BAT = bioavailable testosterone.

Log rank, $P=0.007$, HR 2.2 (1.2-3.9)

BAT $>2.6$ nmol/L (n=736)
BAT $<2.6$ nmol/L (n=194)
The Dilemma

- Natural process?
- Medically significant condition resulting in detriment to quality of life and adversely affecting the function of multiple organ systems?
- Chemical marker of generalized disease?
- Nonconclusive evidence that these diseases are helped with testosterone

Who Should Be Screened for Low Testosterone?

- The Endocrine Society recommends screening for androgen deficiency only in men who present with consistent signs and symptoms of low testosterone levels.
- Subjects with the following conditions should be screened:
  - Sellar mass, radiation to the sellar region, or other diseases of the sellar region
  - Treatment with medications that affect testosterone production or metabolism, such as glucocorticoids and opioids
  - HIV-associated weight loss
  - End-stage renal disease and maintenance hemodialysis
  - Moderate to severe COPD
  - Infertility
  - Osteoporosis or low-trauma fracture, especially in a young man
  - T2DM

COPD = chronic obstructive pulmonary disease. HIV = human immunodeficiency virus.
Patient Presentation

- Harvey, a 58-year-old Caucasian man, presents with a chief complaint of fatigue.
- He reports that he often wakes up in the middle of the night and is unable to go back to sleep.
- He feels depressed and finds it difficult to concentrate at work.
Harvey has been married for 37 years and has 2 adult children.
He works long hours at his accounting firm and frequently eats fast food for lack of time. He has no time to exercise and has been sleeping poorly.

Medical history:
- T2DM
- Hypertension
- Dyslipidemia
Current Medications

- Metformin 500 mg twice daily
- Linagliptin 5 mg daily
- Enalapril 10 mg daily
- Atorvastatin 10 mg daily
Physical Examination

- Neck: No thyromegaly
- Lungs: Clear
- Cor S1S2S4
- Genital: testes descended, no masses, no varicocele, normal size (15-18 g); no prostate nodule palpated
- Feet: no ulcers
- Neurologic: mild decreased sensation to 10-g monofilament; no visual field cuts
- Skin/hair: normal beard, normal male pattern hair in genital axilla
- No gynecomastia

- Height: 5’ 9”
- Weight: 217 lbs
- BMI: 32 kg/m²
- BP: 140/80 mmHg

BMI = body mass index.
Laboratory Results

- A1C: 6.8% at his last check-up 6 months ago
- Cr: 1.3 mg/dL
- PSA: 1.7 ng/mL
- TC: 210 mg/dL
- LDL-C: 110 mg/dL
- HDL-C: 35 mg/dL
- TG: 250 mg/dL
- Microalbumin: undetectable
- GFR: 50 mL/min

A1C = glycated hemoglobin. Cr = creatinine. GFR = glomerular filtration rate. HDL-C = high-density lipoprotein cholesterol. LDL-C = low-density lipoprotein cholesterol. PSA = prostate-specific antigen. TC = total cholesterol. TG = triglyceride.
Harvey, a 58-year-old Caucasian man, presents with a chief complaint of **fatigue**.

- He reports that he often wakes up in the middle of the night and is unable to go back to sleep.
- He feels **depressed** and finds it **difficult to concentrate at work**.
Patient Evaluation and Medical History

- Harvey has been married for 37 years and has 2 children
- He works long hours at his accounting firm and frequently eats fast food for lack of time. He has no time to exercise and has been sleeping poorly
- Medical history:
  - T2DM
  - Hypertension
  - Dyslipidemia
Symptoms and Signs Suggestive of Hypogonadism: FACTS

- No symptoms are unique to hypogonadism
- Screening with testosterone level is appropriate when presented with symptoms
- Diagnosis of hypogonadism is made when one or more symptoms are combined with low testosterone concentration

## Symptoms and Signs Suggestive of Hypogonadism

### More-specific Symptoms and Signs

- Incomplete of delayed sexual development
- Reduced libido
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body hair (axillary or pubic), reduced shaving
- Very small (< 5mL) or shrinking testis
- Inability to father children (azoospermia, oligospermia)
- Height loss, osteoporosis, low trauma fracture, low BMD
- Hot flushes, sweats

BMD = bone mineral density.
### Symptoms and Signs Suggestive of Hypogonadism (cont’d)

<table>
<thead>
<tr>
<th>Less-specific Symptoms and Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased energy, motivation, initiative, and self-confidence</td>
</tr>
<tr>
<td>• Feeling sad or blue, depressed mood, dysthymia</td>
</tr>
<tr>
<td>• Poor concentration and memory</td>
</tr>
<tr>
<td>• Sleep disturbance, increased sleepiness</td>
</tr>
<tr>
<td>• Mild anemia (normochromic, normocytic, in the female range)</td>
</tr>
<tr>
<td>• Reduced muscle bulk and strength</td>
</tr>
<tr>
<td>• Increased body fat, BMI</td>
</tr>
<tr>
<td>• Diminished physical or work performance</td>
</tr>
</tbody>
</table>

Chronic Illness Lowers Testosterone Levels

- T2DM, metabolic syndrome, hypertension, obesity
- Steroid use
- Moderate-to-severe COPD
- Sellar mass, radiation to the sellar region, or other diseases of the sellar region
- End-stage renal disease, maintenance hemodialysis
- HIV-associated weight loss

Hypogonadism and Chronic Opioid Use

- Up to 86% of men treated with chronic opioids may have hypogonadism.
- Chronic opioid use affects the endocrine system, increasing the risk of testicular hypogonadism, hypothyroidism, and osteoporosis.
- Men requiring chronic opioid therapy:
  - Should be assisted in eliminating chronic use of opioids unless absolutely necessary and supervised by an appropriate healthcare provider.
  - Require routine testosterone, thyroid hormone levels, and BMD assessments.
  - May benefit from TRT if serum levels are decreased.

TRT = testosterone replacement therapy.
Common Comorbidities of Hypogonadism

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>2.38</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.09</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.84</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.47</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.41</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>1.40</td>
</tr>
</tbody>
</table>

Screening for Low Testosterone

ADAM Questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have a decrease in libido (sex drive)?</td>
<td>6. Are you sad and/or grumpy?</td>
</tr>
<tr>
<td>2. Do you have a lack of energy?</td>
<td>7. Are your erections less strong?</td>
</tr>
<tr>
<td>3. Do you have a decrease in strength and/or endurance?</td>
<td>8. Have you noticed a recent deterioration in your ability to play sports?</td>
</tr>
<tr>
<td>4. Have you lost height?</td>
<td>9. Are you falling asleep after dinner?</td>
</tr>
<tr>
<td>5. Have you noticed a decreased enjoyment of life?</td>
<td>10. Has there been a recent deterioration in your work performance?</td>
</tr>
</tbody>
</table>

- The patient may have low testosterone if the answer is “yes” to question 1 or 7, or at least 3 of the other questions.
- Aging Male Symptoms questionnaire is a similar questionnaire\(^3\).
- These questionnaires have limited sensitivity in detecting actual androgen deficiency; further physical examinations and hormonal measurements should be obtained in patients with suspected low testosterone.

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Making the Lab Diagnosis
The Hypothalamic-Pituitary-Testicular Axis

FSH = follicle-stimulating hormone. GnRH = gonadotropin-releasing hormone. LH = luteinizing hormone.

Testosterone in the Blood

- Testosterone bound to SHBG
- Testosterone bound to albumin
- Free Testosterone

SHBG = sex hormone-binding globulin.
Not All Testosterone is Available

Free + Bound to Albumin = BAT

Bound to SHBG = Not Available

What Is Considered to Be a Low Serum Testosterone Level?

- Total testosterone <300 ng/dL*
- Free testosterone <50 pg/mL
- Bioavailable testosterone <70 ng/dL

*Total testosterone is the most frequently used lab test for the diagnosis of hypogonadism in the medical literature

Making the Diagnosis

Symptoms

Patient with suspected low T

History and physical exam

Low TT

Normal TT

Remeasure morning TT

<300 ng/dL

>300 ng/dL

Normal TT

Refer to endocrinologist

Low TT

<300 ng/dL

Diagnosis of hypogonadism

Normal TT

Seek other causes

<300 ng/dL

>300 ng/dL

TT = total testosterone.

Primary Hypogonadism: Hypergonadotropic Hypogonadism

- What occurs?
  - Testicular dysfunction
  - Normal hypothalamic/pituitary function

- What results are seen?
  - Low testosterone levels
  - Impairment of spermatogenesis
  - Elevated gonadotropin levels

- Possible cause?
  - Karyotype to rule out Klinefelter’s

Secondary Hypogonadism: Hypogonadotropic Hypogonadism (cont’d)

- **What occurs?**
  - Normal testicular function
  - Hypothalamic/pituitary dysfunction

- **What results are seen?**
  - Low testosterone levels
  - Impairment of spermatogenesis
  - Low or low-normal gonadotropin levels

- **Possible cause?**
  - Infiltrative disease (eg, check iron, TIBC)
  - Age-related androgen deficiency

TIBC = total iron-binding capacity.
Combined Primary and Secondary Mixed Hypogonadism

- **What occurs?**
  - Testicular dysfunction
  - Hypothalamic/pituitary dysfunction

- **What results are seen?**
  - Low testosterone levels
  - Impairment of spermatogenesis
  - Low or low-normal gonadotropin levels (variable)

- **Possible causes:**
  - Age-related androgen deficiency, alcohol. Glucocorticoids, chronic infections (HIV), hemochromatosis, systemic disease

Harvey’s Laboratory Results

- First TT: 230 ng/dL
- Second TT: 243ng/dL
- LH: 7.2 IU
Summary of 2010 Endocrine Guidelines

| Diagnose                      | Only in men with consistent signs and unequivocally low serum testosterone levels  
<table>
<thead>
<tr>
<th></th>
<th>Do not screen in general population; however, consider measurement in disease conditions with high prevalence</th>
</tr>
</thead>
</table>
| Measure                       | Morning total testosterone level  
|                               | Confirm abnormal level and, if in question, assess free or bioavailable testosterone |
| Treatment Goals               | Induce and maintain secondary sex characteristics as well as sexual function  
|                               | Improve sense of well-being  
|                               | Improve muscle mass and strength, and BMD |

In the presence of a clinical picture of androgen deficiency and borderline serum total or free testosterone levels, a short (eg, 3 months) therapeutic trial may be justified.

Consider discontinuing testosterone treatment if no clinical improvement.

Contraindications in Using Testosterone

- Male breast cancer
- Prostate cancer: but not absolute
- Known allergic reactions or sensitivities to substrates used in all types of TRT

Precautions in Using Testosterone

- BPH or LUTS
- Edema in patients with preexisting cardiac, renal, or hepatic disease
- Gynecomastia
- Precipitation or worsening of sleep apnea
- Azoospermia; testicular atrophy
- Erythrocytosis

BPH = benign prostatic hyperplasia. LUTS = lower urinary tract symptoms.
Results of Therapy: FACTS

- Restore sexual functioning and libido
- Restore sense of well-being
- Prevent loss or improve bone density
- Restore muscle mass and strength
- Improves mood

Results of Therapy: Expert Opinion, Not Expert Evidence

- Improvement in insulin resistance
- Decrease abdominal fat
- Decrease cardiovascular risk factors
- Decrease overall mortality

Common Sense in Initiating Testosterone

- Joint decision of informed patient and provider
- Short-acting preparations are better in the beginning to assess tolerability
- Start low and go slow

Treatment Options

- Intramuscular injections
- Transdermal patches
- Transdermal gels
- Buccal tablets
- Subcutaneous pellets

### Intramuscular Injections

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>History (available for 50 years)</td>
<td>Pain</td>
</tr>
<tr>
<td>Self administration</td>
<td>Frequency of injections (every 2-4 weeks)</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>Symptomatic peaks and troughs resulting in variations in breast tenderness, libido, emotional stability, energy</td>
</tr>
<tr>
<td>Flexibility of dosing</td>
<td></td>
</tr>
</tbody>
</table>
## Transdermal Patches

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-scrotal patches</td>
<td>Scrotal patches</td>
</tr>
<tr>
<td>Night-time application results in good approximation of normal circadian plasma testosterone levels</td>
<td>Skin irritation</td>
</tr>
<tr>
<td>Flexibility of dosing</td>
<td></td>
</tr>
</tbody>
</table>

# Transdermal Gels

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application sites (upper arms, shoulder, axilla)</td>
<td>Transfer to others (risk is minimized with high-dose, low-volume preparations)</td>
</tr>
<tr>
<td>Low skin irritation</td>
<td>Low skin irritation</td>
</tr>
<tr>
<td>Invisibility of application</td>
<td></td>
</tr>
<tr>
<td>Flexibility of dosing</td>
<td></td>
</tr>
<tr>
<td>Various concentrations</td>
<td></td>
</tr>
</tbody>
</table>

## Buccal Tablets

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site</td>
<td>Application site</td>
</tr>
<tr>
<td>Relative invisibility</td>
<td>Inadvertent loss of tablet</td>
</tr>
<tr>
<td>Bypass first-pass hepatic metabolism</td>
<td>Gum and buccal irritation, alteration in taste</td>
</tr>
<tr>
<td>Slow release</td>
<td>Twice-daily dosing</td>
</tr>
<tr>
<td></td>
<td>No dose titration</td>
</tr>
</tbody>
</table>

## Subcutaneous Pellets

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>History (started in 1940s)</td>
<td>Painful application</td>
</tr>
<tr>
<td>Relative invisibility</td>
<td>Surgical procedure unlikely to be used by primary care physician</td>
</tr>
<tr>
<td>Long acting</td>
<td>Long acting</td>
</tr>
<tr>
<td>Slow release</td>
<td>Inconvenient removal</td>
</tr>
<tr>
<td></td>
<td>No dose titration</td>
</tr>
<tr>
<td></td>
<td>Procedure can result in infection, fibrosis, or pellet extrusion</td>
</tr>
</tbody>
</table>

### Monitoring Therapy (Part 1)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Evaluate response 3-6 months after treatment initiation and then annually</td>
</tr>
</tbody>
</table>
| Measuring Testosterone | • 3-6 months after initiation  
                   | • Aim to raise level into mid-normal range  
                   | • Monitoring guidelines depend on chosen therapy                           |
| Hematocrit        | Check at 3-6 months, then annually                                          |
| Osteoporosis      | Measure BMD after 1-2 years                                                 |

### Prostate
- DRE at 3 months, then yearly
- In men >40 years, check baseline PSA, at 3-6 months and then in accordance with guidelines

### Urologic Consultation
- PSA increase >1.4 ng/mL in any 12-month period
- PSA velocity of >0.4 ng/mL-yr after 6 months of therapy
- Detection of abnormality on DRE
- AUA/IPSS score of >19

### Adverse Effects
- At each visit
- Can be formulation specific

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## Measuring Testosterone: When to Check

<table>
<thead>
<tr>
<th>Administration Type</th>
<th>Timing for Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable Testosterone – Enanthate or Cypionate</td>
<td>Measure level midway between injections</td>
</tr>
<tr>
<td>Transdermal Patches</td>
<td>Assess level 3-12 hours after application</td>
</tr>
<tr>
<td>Buccal Tablets</td>
<td>Assess immediately before or after application of fresh system</td>
</tr>
<tr>
<td>Transdermal Gels</td>
<td>Any time after patient has been on for a week</td>
</tr>
</tbody>
</table>
| Testosterone Pellets                  | Measure at end of dosing interval  
|                                       | Adjust pellets or interval |

Potential Urologic Adverse Effects of Testosterone Replacement

- Worsening of LUTS
- Rise in PSA
- Testicular atrophy/infertility
- Progression of undiagnosed prostate cancer

Potential Systemic Adverse Effects of Testosterone Replacement

- Erythrocytosis
- Acne and oily skin
- Gynecomastia
- Male pattern balding (familial)
- Growth of breast cancer
- Induction or worsening of obstructive sleep apnea
- Edema in patients with preexisting cardiac, renal, or hepatic disease

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

BPH and Testosterone Therapy: FACTS

- Patients with BPH treated with testosterone are at increased risk of worsening signs or symptoms
- Correlation of voiding volume to prostate size is poor
- Prostate size may increase in first 6 months, but generally to normal volume seen in eugonadal men
- Monitoring is strongly advised

Testosterone Deficiency and Cardiovascular Disease
Testosterone and CV Risk in Men: A Systemic Review and Meta-analysis of Randomized Placebo — Controlled Trials

- Authors point out that many of the studies had limitations: limited reporting of methods; few patients; brief duration – only 4 trials followed patients ≥1 year, 9% loss to follow-up; trials failing to report data on measured outcomes

- **Results:** exogenous testosterone given to men with low T levels had insignificant changes in blood pressure, glycemia, and lipid parameters

- Odds ratio between testosterone therapy and any cardiovascular event was 1.82 (95% CI = 0.78-4.23) but not statistically significant

- **Conclusion of Authors**
  “Testosterone was not associated with important CV events
  … patients and clinicians need large randomized trials of men at risk for CV disease to better inform the safety of long-term testosterone use”
Testosterone Therapy Effects: Systematic Review and Meta-analysis

- Meta-analysis of 51 studies
- Follow-up ranged from 3 months to 3 years
- No significant effect on mortality, prostate, or CV outcomes
- Testosterone treatment was associated with:
  - Significant increase in hemoglobin (WMD, 0.80 g/dL; 95% CI), 0.45 to 1.14] and hematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01).
  - Decrease in HDL (WMD, -0.49 mg/dl; 95% CI, -0.85 to -0.13).
- These findings are of unknown clinical significance
- Current evidence about the safety of testosterone treatment in men in terms of patient-important outcomes is of low quality and is hampered by the brief study follow-up

WMD = weighted mean difference. OR = odds ratio.
1031 men aged >40 years, testosterone <250 ng/dL

Mortality: 10.3% treated, 20.7% untreated ($P<.0001$)

Survival of Treated vs Untreated Testosterone-deficient Men in VA Population: Does TRT Improve Mortality?

VA = US Department of Veterans Affairs.
TOM Trial: Study Design

- Effect of testosterone therapy on lower-extremity strength and physical function in older, hypogonadal men with limitations in mobility
- Men aged ≥65 y (mean, 74 y) with serum TT 100-350 ng/dL or FT <50 pg/mL
- 209 participants randomized to receive testosterone gel or placebo for 12 months
- Testosterone gel titrated from 50 to 150 mg/d, based on serum testosterone level
- After dose adjustment, 16 men received 150 mg/d, 61 received 100 mg/d, and 29 received 50 mg/d
- Mean serum testosterone levels achieved were 574 (403) ng/dL in treatment group and 292 (160) ng/dL in placebo group
- Both groups had high prevalence of hypertension, obesity, diabetes, hyperlipidemia, and CVD

CVD = cardiovascular disease. FT = free testosterone.
TOM Trial: Outcomes Show Benefit

Absolute treatment differences (testosterone vs placebo arms) are plotted for primary and secondary outcomes in units normalized to baseline standard deviation of measurement. Data are point estimates with 95% confidence intervals.

ALST = appendicular lean soft tissue. SD = standard deviation.

TOM Trial: Safety

- In treatment arm, hematocrit and hemoglobin levels increased significantly, and HDL and LDL levels decreased
- TOM trial reported more cardiovascular AEs
  - 23 men receiving testosterone vs 5 receiving placebo
- Cardiovascular AEs had variable clinical importance
- Based on significantly increased incidence of cardiovascular AEs in treatment arm, data and safety monitoring board recommended cessation of enrollment and testosterone therapy:
  - Termination of study in December 2009

AE = adverse event.
**Association of TRT with Mortality, MI, and Stroke**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Retrospective VA study of men with low testosterone levels (&lt;300 ng/dL) who underwent coronary angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>1223 patients started testosterone after a median of 531 days following angiography</td>
</tr>
<tr>
<td></td>
<td>7486 patients received no testosterone</td>
</tr>
<tr>
<td>Results</td>
<td>3 years after coronary arteriography, the Kaplan-Meier estimated cumulative percentages with events were 19.9% in the control group vs 25.7% in the TRT group</td>
</tr>
<tr>
<td></td>
<td>Absolute risk difference of 5.8% at 3 years after coronary angiography</td>
</tr>
<tr>
<td></td>
<td>No difference in effect among those with and without coronary artery disease</td>
</tr>
</tbody>
</table>

MI = myocardial infarction.

Proportion of All Events after Statistical Modeling: VIGEN Study

Proportion of All Events in Patients with Hypogonadism (%) with or Without TRT: VIGEN Study

# Increased Risk of Non-fatal MI Following Testosterone Prescription

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Retrospective cohort study of the risk of acute non-fatal MI in the 90 days following testosterone prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>55,593 patients started testosterone compared to 167,279 prescribed PDE5 inhibitors</td>
</tr>
<tr>
<td>Results</td>
<td>In men &lt;65 years, excess risk was confined to those with prior heart history, relative risk (RR) of 2.9 (1.49, 5.62)</td>
</tr>
<tr>
<td></td>
<td>In men &gt;65 years, the 2-fold increased risk was associated with testosterone prescription regardless of CV history</td>
</tr>
</tbody>
</table>

PDE5 = phosphodiesterase type 5.  
Endocrine Society Statement Regarding Cardiovascular Risk

- Longer, large-scale prospective randomized controlled trials on testosterone therapy are needed
- Physicians and patients should have a conversation about the risks and benefits of using testosterone
- It may be prudent “not to administer testosterone therapy to men who have had a cardiovascular event (MI, stroke, or acute coronary syndrome) in the preceding 6 months.”

Testosterone Deficiency and Diabetes
## Effects on Insulin Resistance From Testosterone Therapy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>• A 12-month, multicenter, prospective, randomized, double-blind, placebo-controlled study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>• 220 men with hypogonadism with T2DM and metabolic syndrome</td>
</tr>
<tr>
<td>Results</td>
<td>• <strong>Significantly improved</strong> insulin resistance in all patients (by 15.2% at 6 months and by 16.4% at 12 months)</td>
</tr>
<tr>
<td></td>
<td>• <strong>Significantly improved</strong> HDL (-0.049 mmol/L) and LDL-C (-0.210 mmol/L), lipoprotein a (-0.31 mmol/L) in selected groups</td>
</tr>
<tr>
<td></td>
<td>• <strong>Significantly improved</strong> sexual health (increase of 4.8 on IIEF)</td>
</tr>
</tbody>
</table>

IIEF = International Index of Erectile Function.  
### Study Design
- 30-week double-blind, placebo-controlled study of long-acting testosterone undecanoate

### Population
- 211 males with T2DM

### Results
- **Significantly improved** A1C at 6 and 18 weeks
- **Significant reduction** in waist circumference, weight and BMI related to achieving adequate serum testosterone levels
- **Significance not reached** in patients with depression

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Conclusions
Conclusions

- Hypogonadism is very prevalent, underdiagnosed and undertreated
- Hypogonadism is associated with major illnesses such as metabolic syndrome, T2DM, and increased mortality
- Indications for referral include change in DRE or PSA, HCT, worsening of voiding symptoms or infertility
- There is no increased risk of prostate cancer from TRT
Found no evidence that testosterone therapy increases cardiovascular risk. On the contrary the weight of evidence accumulated by researches around the world over several decades clearly indicate that higher levels of testosterone are associated with amelioration of cardiovascular risk factor and reduced risk of mortality.
Best Practices Pearls

- Utilize lab testing in appropriate patients who have complaints consistent with the often subtle signs and symptoms of hypogonadism.

- Select testosterone replacement therapy based on patient preference and safety in patients with hypogonadism.

- Monitor the effectiveness and side effects of testosterone replacement therapy in your patients being treated for hypogonadism with testosterone replacement therapy.