“T Party” – Should We Protest the Use of Testosterone Therapy?

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Objectives

• Describe the epidemiology and proper diagnosis of hypogonadism in men
• Report current recommendations for testosterone replacement therapy (TRT)
• Assess the link between TRT and major adverse cardiovascular events (MACE)
• Provide recommendations on proper testosterone use in hypogonadal men

Patient Case

• DT is a 62 year old male presenting to his outpatient clinic
  – CC: “I just don’t have the energy or desire to do anything”
  – PMH:
    • Hypertension, hyperlipidemia, type 2 diabetes, obesity, depression, osteopenia, and recently diagnosed hypogonadism
  – Medications:
    • Lisinopril, hydrochlorothiazide, atorvastatin, metformin, and escitalopram

What else do you want to know?
**Hypogonadism**

- **The Endocrine Society**
  - Failure of the testes to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular (HPT) axis

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**Diagnosis**

- **Symptoms**
- **History and physical exam**
  - Patient with suspected low T
  - Measure morning TT levels
  - Low T
    - <300 ng/dL
    - >300 ng/dL
  - Normal T
    - >300 ng/dL
  - Seek other causes
  - Refer to endocrinologist
  - Diagnosis of hypogonadism

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**Treatment**

- **Supplement testosterone**
  - TRT (e.g., intramuscular, transdermal, subcutaneous)

- **Contraindications**
  - Absolute: Prostate or breast cancer
  - Relative: Elevated hematocrit, severe untreated sleep apnea, unstable congestive heart failure, and severe lower urinary tract symptoms

- **Goal**
  - Replace to mid-normal testosterone levels
  - Monitor
Epidemiology

• Age
  – Gradual decrease in testosterone after ~30 years of age

• Prevalence
  – 6 – 12% for men aged 40 – 60 years

• Risk factors
  – Acute
  – Chronic

Testosterone Prescribing Pattern

2011
$1.6 billion

1980s
$18 million

Cardiovascular (CV) Risk

Low Testosterone

• Metabolic syndrome
• Hypertension
• Atherosclerosis
• Dyslipidemia
• Inflammation
• Osteopenia

Testosterone Therapy

• Increased hematocrit & blood viscosity
• Increased estrogen
• Increased platelet aggregation
• Reduced fibrinolytic enzymes
• Reduced HDL cholesterol

Controversy

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF TESTOSTERONE AND CARDIOVASCULAR RISK

Neil Goodman, MD, FACE; Andre Guay, MD, FACE; Parshak Dandona, MD, PhD, FACE; Sandeep Dhindsa, MD; Charles Faiman, MD, MACE; Glenn R. Cunningham, MD; for the AACE Reproductive Endocrinology Scientific Committee

Literature Review

• Objective
  – Does the use of testosterone replacement therapy increase the risk of MACE in hypogonadal men?


Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels.

*JAMA* 2013; 310:1829-36.
Objective
Assess the association between total testosterone (TT) and all-cause mortality, myocardial infarction (MI), or stroke

Design
Retrospective cohort study using Veterans Affairs (VA) database

Population
Male veterans with TT levels less than 300 ng/dL and a history of coronary angiography completed between 2005 – 2011
- TRT:
  - Mean age (yrs): 61
  - Mean TT (ng/dL): 176
- Untreated:
  - Mean age (yrs): 64
  - Mean TT (ng/dL): 207

Intervention (n = 8,709)
TRT (n = 1,223) vs. Untreated (n = 7,486)
- Mean follow-up (months): 27.5

Absolute Outcomes

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mortality</th>
<th>MI</th>
<th>Stroke</th>
<th>Composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRT (n = 1,223)</td>
<td>67 (5.5%)</td>
<td>23 (1.9%)</td>
<td>33 (2.7%)</td>
<td>10.1%</td>
</tr>
<tr>
<td>Untreated (n = 7,486)</td>
<td>681 (9.1%)</td>
<td>420 (5.6%)</td>
<td>486 (6.5%)</td>
<td>21.2%</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan-Meier Survival Curves With Testosterone Therapy Evaluated as a Time-Varying Covariate

Vigen et al. (2013) (cont.)

Strengths
- Sensitivity analyses
- VA database
- High CV-risk population

Limitations
- Retrospective database review
- Differing baseline characteristics
- Patient prescription rates utilized for defining treatment
- Fairly short treatment duration and follow-up
- Repeat TT levels not always assessed
- Data collection errors

Conclusions
- Shows that TRT may increase the risk of MACE in a high risk population of hypogonadal men

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men.


**Sharma et al. (2015)**

**Objective**
Examine the effect of TRT on cardiovascular outcomes by comparing the incidence of MI, stroke, and all-cause mortality among treated and untreated patients

**Design**
Retrospective cohort study utilizing the VA database

**Population**
Male veterans with TT levels lower than the respective laboratory reference range, collected from 1999 – 2014
• Excluded those with history of MI or ischemic stroke
• Median age (yrs): 66

**Intervention**
(n = 83,010)
1. TRT with a normalized TT (n = 43,931)
2. TRT without a normalized TT reached (n = 25,701)
3. Untreated (n = 13,378)
• Mean follow-up (yrs): 5
• Mean TRT duration for normalized group (yrs): 3

| Table 1: Unadjusted and adjusted hazard ratios for all-cause mortality, MI, and stroke |
|-------------------------------------------------|------------------|------------------|------------------|------------------|
| Model                                           | All-cause mortality | Myocardial infarction | Stroke |
|                                  | Hazard ratio | 95% CI | P     | Hazard ratio | 95% CI | P     | Hazard ratio | 95% CI | P     |
| Univariate                                    |               |        |       |               |        |       |               |        |       |
| Normalized treated vs. untreated (n = 43,931)     | 0.70          | 0.69-0.71 | <0.001 | 0.70          | 0.69-0.70 | <0.001 | 0.81          | 0.78-0.84 | 0.007 |
| Propensity model (weighted probability of treatment) |               |        |       |               |        |       |               |        |       |
| Normalized treated vs. untreated (n = 43,931)     | 0.70          | 0.69-0.71 | <0.001 | 0.70          | 0.69-0.70 | <0.001 | 0.81          | 0.78-0.84 | 0.007 |
| Univariate                                    |               |        |       |               |        |       |               |        |       |
| Normalized treated vs. non-normalized treated (n = 25,701) | 0.70          | 0.67-0.73 | 0.004 | 0.70          | 0.68-0.72 | 0.004 | 0.80          | 0.77-0.83 | 0.009 |
| Propensity model (weighted probability of treatment) |               |        |       |               |        |       |               |        |       |
| Normalized treated vs. non-normalized treated (n = 25,701) | 0.70          | 0.67-0.73 | 0.004 | 0.70          | 0.68-0.72 | 0.004 | 0.80          | 0.77-0.83 | 0.009 |
| Univariate                                    |               |        |       |               |        |       |               |        |       |
| Normalized treated vs. untreated (n = 13,378)     | 0.70          | 0.69-0.71 | <0.001 | 0.70          | 0.69-0.70 | <0.001 | 0.81          | 0.78-0.84 | 0.007 |
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Sharma et al. (2015) (cont.)

Strengths
+ Large sample size and long follow-up period
+ Required repeat low TT measurements for inclusion
+ Institution specific cutoff values for low TT
+ VA database

Limitations
- Retrospective database review
- Excluded patients with prior cardiovascular events
- Patient prescription rates utilized for defining treatment
- Relatively short mean duration of TRT
- Normalized levels not defined

Conclusions
• MACE rates appear to be reduced when testosterone supplementation is used to completely normalize TT levels in a relatively low risk population


Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis.

Objectives

Determine the effect of testosterone supplementation, as compared to placebo, on the incidence of MACE (CV death, non-fatal MI, stroke, acute coronary syndromes, and heart failure).

Design

- Meta-analysis reviewing randomized controlled trials with CV events as primary or secondary outcomes between Jan. 1969 and Jan. 2014
- Searched Medline, Embase, and Cochrane using text and MeSH term “testosterone,” and limited to Clinical Trials, Humans, and English
- Utilized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Study Selection (n = 75)

- Inclusion:
  - All RCTs enrolling men and comparing the effect of testosterone supplementation versus placebo on CV-related events
- Exclusion:
  - Simultaneous treatment with other hormones and drugs
  - Studies not stating the occurrence or absence of CV-related events

Study Characteristics

- 6/75 studies included with CV events as a primary endpoint
- 31/75 studies included hypogonadal patients only
- 47/73 did not detect any MACE outcomes

Baseline Characteristics

<table>
<thead>
<tr>
<th>Total patients</th>
<th>TRT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean trial duration (wks)</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Mean baseline TT (ng/dL)</td>
<td>323</td>
<td>323</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>28.1</td>
<td>28.1</td>
</tr>
</tbody>
</table>

study results and conclusion...
Corona et al. (2014) (cont.)

Results
A causal role between testosterone supplementation and adverse CV events (composite or single events) is not supported

Strengths
+ Utilized controlled trials only
+ Largest number of studies combined to date
+ Tested for effect of drug company influence

Limitations
- Small number of trials with MACE as primary outcome
- Short average trial duration
- Unclear if all TT levels normalized
- Many studies with no events eliminated from analysis
- Quality of the included studies

Conclusions
• Short-term use of TRT is not associated with increased or decreased risk of MACE

Literature Summary

Vigen
• Increased risk of MACE with TRT in high risk hypogonadal men

Sharma
• Decreased risk of MACE with TRT in low risk hypogonadal men

Corona
• Neutral effect on MACE with TRT in a diverse patient population

Recommendations

Diagnosis
• Symptoms of low testosterone with multiple levels drawn correctly

Treatment
• Assess risk factors for MACE
• Thoroughly counsel on potential benefits and risks of TRT
• Provide testosterone therapy for properly diagnosed hypogonadal men who are not at a high risk of MACE

Monitoring
• Obtain normalized testosterone levels
• Trial period lasting 3 months
• Watch for contraindications and adverse effects
Patient Case

DT is a 62 year old male presenting to his outpatient clinic

- CC:
  - “I just don’t have the energy or desire to do anything”

- PMH:
  - Hypertension, hyperlipidemia, type 2 diabetes, obesity, depression, osteopenia, and recently diagnosed hypogonadism

- Medications:
  - Lisinopril, hydrochlorothiazide, atorvastatin, metformin, and escitalopram

Increased risk:
- Age
- Comorbidities
  - Obesity
  - Hypertension
  - Diabetes
  - Dyslipidemia

Decreased risk:
- No history of major adverse cardiovascular events
- No family history of clotting
- No contraindications to TRT
- Non-smoker
- Reasonably controlled comorbidities

Would you recommend TRT?

References

Acknowledgements

• Evaluator:
  – Dr. Lindsay Vasquez, PharmD, BCPS, BCACP, CDE

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  – Dr. Evan Peterson, PharmD, BCPS
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