Adult Onset Hypogonadism: Implications for Care of the Aging Male Population

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Disclosures

- Consultant - Abbvie, Boston Scientific, Coloplast, Endo
Does Aging Alone Cause a Significant Decline in Testosterone Levels?
Prevalence of Androgen Deficiency

Overall, 38.7% of men >45y have T-levels<300 ng/mL

Prevalence of hypogonadism in males aged at least 45 years: the HIM study

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hypogonadal patients (n = 836)</th>
<th>Eugonadal patients (n = 1326)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>547 (65.4)</td>
<td>678 (51.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>506 (60.5)</td>
<td>670 (50.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>258 (30.9)</td>
<td>237 (17.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>270 (32.3)</td>
<td>225 (17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostatic disease/disorder</td>
<td>165 (19.7)</td>
<td>226 (17.0)</td>
<td>0.121</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>155 (18.5)</td>
<td>211 (16.0)</td>
<td>0.113</td>
</tr>
<tr>
<td>Insomnia/sleep disturbance</td>
<td>129 (15.4)</td>
<td>185 (14.0)</td>
<td>0.342</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>102 (12.2)</td>
<td>118 (8.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>Headaches (within the last 2 weeks)</td>
<td>70 (8.4)</td>
<td>125 (9.4)</td>
<td>0.405</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>28 (3.3)</td>
<td>29 (2.2)</td>
<td>0.101</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>15 (1.8)</td>
<td>15 (1.1)</td>
<td>0.199</td>
</tr>
<tr>
<td>Not reported</td>
<td>0 (0.0)</td>
<td>4 (0.3)</td>
<td>nr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factor/condition</th>
<th>Hypogonadism prevalence rate (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>52.4 (47.9–56.9)</td>
<td>2.38 (1.93–2.93)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50.0 (45.5–54.5)</td>
<td>2.09 (1.70–2.58)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42.4 (39.6–45.2)</td>
<td>1.84 (1.53–2.22)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>47.3 (34.1–60.5)</td>
<td>1.59 (0.92–2.72)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>40.4 (37.6–43.3)</td>
<td>1.47 (1.23–1.76)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>44.4 (25.5–64.7)</td>
<td>1.41 (0.64–3.01)</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>43.5 (36.8–50.3)</td>
<td>1.40 (1.04–1.86)</td>
</tr>
<tr>
<td>Prostatic disease/disorder</td>
<td>41.3 (36.4–46.2)</td>
<td>1.29 (1.03–1.62)</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>38.8 (33.7–44.0)</td>
<td>1.13 (0.89–1.44)</td>
</tr>
<tr>
<td>Headaches (within last 2 weeks)</td>
<td>32.1 (25.3–38.8)</td>
<td>0.81 (0.58–1.11)</td>
</tr>
</tbody>
</table>
Testosterone and Aging

- Serum total T starts to decrease between the ages of 30 of 55 years by 1–2% per year
  - Number of Leydig cells and amount of testosterone production and secretion from Leydig cells significantly decline
  - Impairment of GnRH secretion results in decreased LH pulse frequency and amplitude
- Metabolic clearance rate of testosterone decreases with aging, lessening the impact of reduced testosterone production on circulating testosterone concentrations
- Sex hormone-binding globulin (SHBG) increases by 2–3% per year
- Thus free T decreases more than total T, approximately by 2–3% per year

Dhindsa et al Endocr Pract. 2018 Apr;24(4):375-385
Age-Specific Population Centiles for Androgen Status in Men

- 10,904 serum samples (from observational population-based studies in three major cities across Australia)
- T, DHT, and E2 decline gradually from ages 35 onwards with a more marked decline after 80 years of age
- Higher weight, BMI, and body surface area as well as shorter stature are associated with reduced serum testosterone, DHT, and E2

The Relative Contributions of Aging, Health, and Lifestyle Factors to Serum Testosterone Decline in Men

- Prospective cohort study of 1667 men aged 40 to 70 at baseline
- Follow-up up to 17 years
- Main outcome measures: total serum T, calculated free T (FT), and SHBG
European Male Aging Study (EMAS) 
Relation Between Age and Testosterone

European Male Aging Study (EMAS)
Relation Between age and Testosterone

Shared Risk Factors Between Hypogonadism and Metabolic Syndrome

Androgen deficiency “hypogonadism”

Obesity  Hypertension  Dyslipidemia  Hyperglycemia  Insulin resistance

Metabolic syndrome

Adapted from Traish, J Androl 2009
Prevalence of the Metabolic Syndrome Among US adults

Prevalence of Obesity Rises with Age

Obesity by Age Group -- 2008 vs. 2012

Gallup-Healthways Well-Being Index
Misconceptions!

Male Menopause: Facts and Symptoms

TIME
Manopause?!
Aging, Insecurity and the $2 billion testosterone industry
by David Von Drehle

Signs of Male Menopause (Andropause)
“Andropause is a gradual decline in hormone levels. When men reach about 40, testosterone levels usually begin to drop about one percent a year.”

The following are some symptoms of low testosterone:
- diminished sex drive
- reduced muscle bulk and strength
- night sweats
- fewer spontaneous erections
- poor concentration
- sleep problems
- loss of body hair
- palpitations
- shrunken testes
- height loss
- fatigue
- irritability
- memory loss
- increased body fat
- reduced self-confidence
- infertility
- depression
- swollen breasts
- anemia

Male Aging Facts
- Testosterone production/levels decrease gradually beginning around age 30
- Sperm production does not stop
- Not all men experience low testosterone and sperm production

Female Menopause Facts
- Estrogen (female sex hormone) production drops rapidly beginning around age 40
- Egg production stops completely
- All women experience low estrogen and egg production
"Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.

a) Primary hypogonadism (congenital or acquired)-testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy.

b) Hypogonadotropin hypogonadism (congenital or acquired)—idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation."
FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use

This information is an update to the FDA Drug Safety Communication: FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on January 31, 2014.

Safety Announcement

[03-03-2015] The U.S. Food and Drug Administration (FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man’s symptoms seem related to low testosterone. We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. We are also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests.
1 INDICATIONS AND USAGE

AndroGel 1% is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.

- Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.
Prevalence of Hypogonadism

- 79.4% Eugondal
- 17.4% Secondary
- 3.2% Primary

Specific medical conditions:
- 50.4% Unknown
- 49.6% Specific medical conditions

Specific Medical Conditions Associated with Secondary Hypogonadism

- 89.1% Unknown
- 10.9% Specific medical conditions
- 70.7% Associated with concomitant metabolic disease (Obesity, T2DM or Metabolic Syndrome)
- 29.3% Unknown

Corona et al J Sex Med 2015; 12 1690-1693)
• AOH is a clinical and biochemical syndrome characterized by a deficiency of testosterone with signs and symptoms that can be caused by testicular and/or hypothalamic-pituitary dysfunction

• AOH is clinically distinct from classical primary and secondary hypogonadism

• AOH more often occurs in men who have developed chronic medical conditions
Benefit of Testosterone Therapy in Older AOH Patients
# Physiologic Changes Consistent with Androgen Deficiency in Older Men

## Body Composition
- $\downarrow$ Lean body mass
- $\uparrow$ Fat mass
- $\downarrow$ Muscle mass and strength
- $\downarrow$ Bone mineral density

## Brain Function
- $\downarrow$ Libido
- $\downarrow$ Erections
- $\uparrow$ Depression
- $\downarrow$ Cognitive function
- $\downarrow$ Sleep quality
Effects of Testosterone Treatment in Older Men


*for the Testosterone Trials Investigators*

- 790 men 65 years or older
- T<275ng/dl and hypogonadal symptoms
- T gel or placebo for 12 months
- Participated in 1 or more of 3 trials
  - Sexual Function Trial
  - Physical Function Trial
  - Vitality Trial
- Other T Trials:
  - Cardiovascular, Bone, Anemia, Cognition

# Results of the T Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary outcome measure</th>
<th>Number enrolled</th>
<th>Result after treatment with testosterone gel for 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Function Trial</td>
<td>Change in Psychosexual Daily Questionnaire Question 4</td>
<td>459</td>
<td>The mean difference in the change from baseline between participants assigned to testosterone and those assigned to placebo, 0.58; <em>P</em> &lt; .001</td>
</tr>
<tr>
<td>Physical Function Trial</td>
<td>The 6-Minute Walk Test</td>
<td>387</td>
<td>No benefit: no significant difference between groups in the percentage of men whose 6-minute walking distance increased by at least 50 meters (OR, 1.42; <em>P</em> = .20)</td>
</tr>
<tr>
<td>Vitality Trial</td>
<td>Increase in Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Score ≥ 4 points</td>
<td>474</td>
<td>No benefit: no significant difference between groups, as determined by an increase of at least 4 points in the FACIT–Fatigue score (OR, 1.23; <em>P</em> = .30)</td>
</tr>
<tr>
<td>Cardiovascular Trial</td>
<td>Impact on Noncalcified Coronary Artery Plaque Volume</td>
<td>170</td>
<td>Significantly greater increase in coronary artery noncalcified plaque volume (estimated difference, 41 mm^3; 95% CI, 14 mm^3 to 67 mm^3; <em>P</em> = .003)</td>
</tr>
<tr>
<td>Bone Trial</td>
<td>Volumetric Bone Mineral Density (vBMD) of Spine Trabecular Bone by Quantitative Computed Tomography</td>
<td>211</td>
<td>Significantly greater increase than placebo in mean spine trabecular vBMD (treatment effect, 6.8%; 95% CI, 4.8% to 8.7%; <em>P</em> &lt; .001)</td>
</tr>
<tr>
<td>Cognitive Function Trial</td>
<td>Delayed Paragraph Recall Wechsler Memory Scale Revised Logical Memory II</td>
<td>493</td>
<td>No benefit: no significant improvement in memory (adjusted estimated difference, −0.07 [95% CI, −0.92 to 0.79]; <em>P</em> = .88) or other cognitive functions</td>
</tr>
<tr>
<td>Anemia Trial</td>
<td>Effect of Testosterone on Hemoglobin Levels in Unexplained Anemia</td>
<td>62</td>
<td>Significant increase in the percentage whose hemoglobin concentration improved by 1.0 g/dL or more over the baseline value more than placebo (adjusted OR, 31.5; 95% CI, 3.7 to 277.8; <em>P</em> = .002)</td>
</tr>
</tbody>
</table>
T Trials: Physical Function Test

- **Primary Outcome**
  - Percentage of men who increased the distance walked in the 6-minute walk by at least 50 meters

- **Secondary Outcome**
  - Changes from baseline in the 6 minute walking distance
  - At least 8 point improvement on Physical-Function domain (PF-10) of the Short Form Health Survey (SF-36)
  - Changes from baseline in PF-10

## Physical Function Trial

<table>
<thead>
<tr>
<th></th>
<th>No. of Men</th>
<th>Baseline</th>
<th>Change at 3 months</th>
<th>Change at 12 months</th>
<th>Treatment Effect</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&gt;50m in 6 min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>191</td>
<td></td>
<td>11.2%</td>
<td>20.3%</td>
<td>1.42(0.83-2.45)</td>
<td>0.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>196</td>
<td></td>
<td>7.8%</td>
<td>12.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6 min walk distance (m)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>191</td>
<td>347.7±69.1</td>
<td>10.2±35.8</td>
<td>14.3±45.9</td>
<td>4.09(-3.0-11.18)</td>
<td>0.28</td>
</tr>
<tr>
<td>Placebo</td>
<td>196</td>
<td>344.9±68.5</td>
<td>4.6±35.2</td>
<td>5.5±46.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Increase of ≥8 on PF-10</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>184</td>
<td></td>
<td>43.8%</td>
<td>38.2%</td>
<td>1.34(0.90-2.00)</td>
<td>0.15</td>
</tr>
<tr>
<td>Placebo</td>
<td>181</td>
<td></td>
<td>34.5%</td>
<td>34.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PF-10 score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>184</td>
<td>65.4±20.0</td>
<td>5.6±15.2</td>
<td>5.8±17.5</td>
<td>2.75(0.20-5.29)</td>
<td>0.03</td>
</tr>
<tr>
<td>Placebo</td>
<td>181</td>
<td>64.8±21.3</td>
<td>4.2±13.7</td>
<td>2.4±17.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Physical Function: All Men in T Trial

<table>
<thead>
<tr>
<th></th>
<th>No. of Men</th>
<th>Baseline</th>
<th>Change at 3 months</th>
<th>Change at 12 months</th>
<th>Treatment Effect</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&gt;50m in 6 min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>392</td>
<td></td>
<td>10.9%</td>
<td>20.5%</td>
<td>1.76(1.21-2.57)</td>
<td>0.003</td>
</tr>
<tr>
<td>Placebo</td>
<td>389</td>
<td></td>
<td>7.0%</td>
<td>12.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6 min walk distance (m)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>392</td>
<td>387.0±81.7</td>
<td>10.9±45.1</td>
<td>13.6±43.4</td>
<td>6.69(1.80-11.57)</td>
<td>0.007</td>
</tr>
<tr>
<td>Placebo</td>
<td>389</td>
<td>387.0±83.7</td>
<td>3.6±43.9</td>
<td>6.4±45.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Increase of ≥8 on PF-10</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>309</td>
<td></td>
<td>38.9%</td>
<td>36.7%</td>
<td>1.50(1.080-2.00)</td>
<td>0.02</td>
</tr>
<tr>
<td>Placebo</td>
<td>305</td>
<td></td>
<td>31.6%</td>
<td>30.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PF-10 score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>309</td>
<td>71.2±20.21</td>
<td>5.0±14.7</td>
<td>4.3±16.9</td>
<td>3.06(1.18-4.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>Placebo</td>
<td>305</td>
<td>64.8±21.3</td>
<td>3.9±12.8</td>
<td>3.3±16.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exogenous Testosterone (T) Alone or with Finasteride Increases Physical Performance, Grip Strength, and Lean Body Mass in Older Men with Low Serum T

- 65 y/o and older hypogonadal men
- Randomized to receive:
  - TE 200mg every 2 weeks
  - TE + Finasteride
  - Placebo
- 36 months

Exogenous Testosterone (T) Alone or with Finasteride Increases Physical Performance, Grip Strength, and Lean Body Mass in Older Men with Low Serum T

A Randomized Pilot Study of Monthly Cycled Testosterone Replacement or Continuous Testosterone Replacement Versus Placebo in Older Men

- 24 men 70 years and older
- Randomized to
  - TE 100mg/month
  - TE 100mg qom
  - Placebo
- 5 months

Sheffield-Moore et al J Clin Endocrinol Metab. 2011 Nov; 96(11): E1831–E1837
A Randomized Pilot Study of Monthly Cycled Testosterone Replacement or Continuous Testosterone Replacement Versus Placebo in Older Men

Sheffield-Moore et al J Clin Endocrinol Metab. 2011 Nov; 96(11): E1831–E1837
Objective: To determine if TTh in hypogonadal men increases volumetric BMD (vBMD) and bone strength in the spine and hip

211 hypogonadal men who participated in the T trial

Outcomes (baseline vs 12 months):

• vBMD (quantitative CT data)
• Bone strength (quantitative CT data)
• Areal BMD (DEXA scan)
Anemia and the Geriatric Patient

- The prevalence of anemia increases from approximately 5% at 65 years to >20% at age 85 years
- Approximately 30% of all anemia cases in the elderly are of unknown etiology
- A reduction in testosterone levels has been suggested as contributing to the development of anemia

Guralnik et al Blood 2004; 104: 2263–2268
Objective: To determine if TTh in hypogonadal men with unexplained anemia would increase their hemoglobin concentration

126 anemic hypogonadal men participating in the T Trial

Outcome: The percent of men with anemia whose hemoglobin levels increased by 1.0 g/dL or more
Results

- TTh resulted in a greater percentage of men with hemoglobin levels increasing by 1.0 g/dL or more over baseline than placebo (54% vs 15%) \((P = 0.002)\)

- Percentage of men who at month 12 were no longer anemic in T group (58.3%) was greater than placebo (22.2%) \((P = 0.002)\)
Adult Onset Hypogonadism: Implications for Care of the Aging Male Population

Benefits (Body Composition)
- Improvement is anemia
- Improvement in muscle mass
- Decreased fat mass
- Improved physical strength
- Improved bone mineral density

Results
- Improved quality of life and overall health
- Decreased falls and injury
- Decreased mortality
Safety of Testosterone Therapy in Older AOH Patients
### T Trial and Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=394)</th>
<th>Testosterone (N=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in PSA by $\geq 1.0$ 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 $\geq 19$</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td><strong>Cardiovascular events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MI, stroke, or death from CV cause</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td><strong>Hemoglobin $\geq 17.5$ g/dl</strong></td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>
A Study to Evaluate the Effect of Testosterone Replacement Therapy (TRT) on the Incidence of Major Adverse Cardiovascular Events (MACE) and Efficacy Measures in Hypogonadal Men (TRAVERSE)

- 6000 participants 45 to 80 years old
- Randomized placebo controlled trial
- Anticipated completion: June 30, 2022
- **Primary outcome:**
  - Time to Major Adverse Cardiac Event (MACE), which includes nonfatal MI, nonfatal stroke or death due to CV causes
- **Secondary outcome:**
  - Cardiovascular safety: incidence of MACE or cardiac revascularization procedures/ cardiac percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)
  - Prostate safety: incidence of high grade prostate cancer
- **Other outcomes:**
  - Sexual function, depression, anemia, bone fractures, diabetes

Clinical Trials.gov identifier: NCT03518034
Conclusion

• Aging alone generally does not contribute to a significant decline in serum T values

• As men age, the development of co-morbid conditions, such as obesity and diabetes, significantly contribute to declining T levels

• Low testosterone is associated with impaired body composition and brain function (i.e depression, libido)

• TTh has been shown to effectively improve body composition and anemia in older men and should be considered in hypogonadal older men to improve their quality of life
Thank You

Texas Medical Center, Houston