Erectile Dysfunction, Cardiovascular Risk and Testosterone

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Robert A. Kloner MD, PhD
Director of the Cardiovascular Research Institute of HMRI
VP of Translation, HMRI
Professor of Clinical Medicine, Division of Cardiovascular Medicine, Dept. of Medicine,
Keck School of Medicine at University of Southern California
Disclosure: Dr. Kloner is a consultant to Pfizer, Abbvie, TesoRx, and Lipocine
Introduction to Topic/Presentation Outline

1. Erectile Dysfunction (ED) is related to CV risk factors
2. ED is common in patients with CAD
3. Low endogenous testosterone levels are associated with CV disease and atherosclerosis
4. There is controversy in the literature regarding the safety of Testosterone Replacement Therapy
5. There is a need for a prospective, controlled, blinded outcome study of T therapy with the primary endpoints being major adverse cardiovascular adverse events (MACE)
The Massachusetts Male Aging Study


- “After adjusting for patient age, the probability of complete ED was 39% in men with treated heart disease, 28% with treated diabetes, and 15% with treated hypertension versus 9.6% in the entire population.”
- A higher probability of impotence was directly correlated with heart disease and inversely correlated with HDL cholesterol
- “Cigarette smoking was associated with a greater probability of complete impotence in men with heart disease and hypertension”
Recent medical studies indicate that cigarettes are one of the leading causes of impotence.

Cigarettes. Still think they’re sexy?

to quit call 1-800-7-NO-BUTTS
Follow-up Study of Massachusetts Male Aging Study

  - no ED at baseline, no diabetes, heart disease, or related medications

- Results of follow-up
  - cigarette smoking at baseline almost doubled likelihood of moderate or complete ED (24% vs 14%, age adjusted; p=0.01)
  - cigar smoking and passive exposure to cigarette smoke predicted ED
  - being overweight (body mass index $\geq 28$ kg/m$^2$) predicted ED
  - a composite coronary risk score predicted ED
  - weaker correlations with hypertension, dietary intake of cholesterol and unsaturated fat

Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study

MM Fung, R Bettencourt, E Barrett-Connor. JACC 2004;43:1405

- Reported that at follow up: “Mean age, body mass index, cholesterol, and triglycerides were each significantly associated with an increased risk of ED.”
- Hypercholesterolemia was a strong independent predictor of ED and was the most common risk factor in men with only one risk factor.
Correlation between erectile function and cardiovascular risk factors by assessing arterial stiffness and myocardial imaging and carotid artery intima-media thickness

- Significant correlation in men with abnormal IIEF-5 scores (International Index of Erectile Function Questionnaire) and pathologic imaging
- Men with abnormal cholesterol and abnormal pulse wave velocity had lower IIEF-5 scores
- Men with abnormal HB1Ac and triglyceride levels had lower IIEF-5 scores

Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction

Showed a 1.32 times risk of ED for every mmol/L of increase in total cholesterol and a 0.38 times risk of ED for every mmol/L of HDL.

Kim SC, et al. investigated the effects of impaired lipid metabolism in the contractile and relaxation responses of rabbit cavernous smooth muscle to clarify its pathogenesis.

They concluded that: “Oxidized LDL is the major causative cholesterol of the impaired relaxation response. A chain reaction, the production of superoxide radicals and functional impairment of eNOS may be a major cause of the functional impairment in the early stages of hypercholesterolemia.”
Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial


Obese men without diabetes, hypertension or hyperlipidemia who had ED (IIEF score ≤ 21) were randomly assigned to intervention (detailed advice on how to achieve a loss of 10% or more in total body weight by reducing calories and increasing activity) or to control (general information about food choices and exercise).
After 2 years, IIEF score improved in the intervention group but remained stable in the control group.

Erectile Dysfunction and Undiagnosed Diabetes, Hypertension, and Hypercholesterolemia

Sean C. Skeldon, Allan S. Detsky, S. Larry Goldenberg, and Michael R. Law, PhD

- Investigated whether ED was associated with cardiometabolic risk factors in US men
- Analyzed data from men ≥ 20 years old who participated in the National Health and Nutrition Examination Study 2001-2004 (n = 4,519)
- Results: found no association between ED and undiagnosed hypertension or undiagnosed hypercholesterolemia. However, men with ED had more than double the odds of having undiagnosed diabetes.

Statins and Male Sexual Health: A Retrospective Cohort Analysis

- Investigated the risk of ED in statin users versus non-users
- Performed a retrospective cohort study (n = 6604) of men aged 30-85. Statin users were defined as those prescribed a statin for ≥ 3 months
- Found that statin use was not significantly associated with an increase or decrease in ED

Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation

• Men (n=9) were determined to have increased cholesterol as the only risk factor for ED. Subjects were given atorvastatin for $3.7 \pm 2.1$ months, with a goal decrease of total cholesterol to less than 200 mg/dl and low-density lipoprotein cholesterol to less than 120 mg/dl.

• Results: Clinically 8 of the 9 men had improved erection adequate for penetration during sexual intercourse. Mean questionnaire scores improved ($p < 0.001$). Mean total and low-density lipoprotein cholesterol decreased significantly after treatment ($p < 0.001$). RigiScan measurements showed an increased average penile rigidity at the base ($p < 0.001$) and tip ($p < 0.005$) after treatment with atorvastatin.

Conclusions of Questionnaire Study

- ED was present in 75% of men with chronic coronary disease and severe in 25%
- ED is very common in the coronary patient (most likely related to the other ED = endothelial dysfunction and atherosclerosis)
- Patients with coronary artery disease or risk factors for CAD should be routinely questioned about their sexual health and ED

Kloner RA et al. Erectile dysfunction in the cardiac patient: How common and should we treat?

J Urology. 2003;170:546
Endothelial Dysfunction is the Final Common Pathway in CVD and ED

Factors:
- Hypertension
- Diabetes
- Dyslipidemia
- Tobacco

Mechanisms:
- Oxidative Stress
- Endothelial Cell Injury
  - Vasoconstriction
  - Plaque Rupture
  - Thrombosis
  - ED
Basic Science Studies of Testosterone and the Heart

Good effects

✓ Decreases action potential duration early after depolarization, shortens QT<sub>C</sub> interval
✓ Neutral effect or reduction of experimental myocardial infarct size.
✓ Opens the mitochondrial kATP channel (cardioprotective)
✓ Enhances vasodilation
✓ Improves lipid metabolism
✓ Reduces insulin resistance
✓ May attenuate atherosclerosis
Basic Science Studies of Testosterone and the Heart

Bad effects

- Vasoconstriction
- Inflammation
- Death signaling (pro-apoptotic)
- Increases in platelet thromboxane A₂ receptor density and aggregation
- Dihydrotestosterone, a metabolite, increases smooth muscle proliferation and vascular cell adhesion molecule expression
Relationship between low testosterone levels and coronary artery disease
Inverse association between testosterone levels and aortic atherosclerosis

Relative Risk

$P_{\text{trend}}=.02.$

BT, bioavailable testosterone; TT, total testosterone.

Effects of chronic testosterone administration on lipid metabolism in elderly male diabetic patients with coronary artery disease

<table>
<thead>
<tr>
<th></th>
<th>Testosterone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 months</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>256±32</td>
<td>239±25*</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>28±6</td>
<td>31±11</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>231±54</td>
<td>199±37*</td>
</tr>
<tr>
<td>Fasting glucose mg/dl</td>
<td>107.8±37</td>
<td>109±38</td>
</tr>
</tbody>
</table>

Lipid profile and glucose blood levels in the testosterone and placebo groups at baseline and three months

*P<0.05

High serum testosterone is associated with reduced risk of CV events in elderly men. The MrOS (Osteoporotic fractures in men) study in Sweden

- 2416 men age 69-81 years
- Both total testosterone and sex-hormone-binding globulin levels were inversely associated with the risk of CV events (trend over quartiles: $p = 0.009$ and $p = 0.012$, respectively).
- Men in highest quartile of testosterone ($\geq 550$ ng/dl) had a lower risk of CV events vs. men in the 3 lower quartiles (HR 0.70, CI=0.56-0.88)
- This association remained after adjustment for traditional CV risk factors
- Conclusion: High serum testosterone predicted a lower 5-year risk of CV events in elderly men.

Hazard ratios for CV events by quartile of total testosterone

Ohlsson C et al. JACC 2011; 58:1674-81
Cardiovascular event rate in randomized, placebo-controlled trials of testosterone included in a meta-analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Testosterone Group: Adverse Event Rate per 1000 Patient-Years*</th>
<th>Placebo Group: Adverse Event Rate per 1000 Patient-Years*</th>
<th>Pooled Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit &gt;50%</td>
<td>64.5</td>
<td>2.8</td>
<td>3.69†</td>
<td>1.82, 7.51</td>
</tr>
<tr>
<td>Atrial fibrillation/arrhythmia</td>
<td>9.2</td>
<td>2.8</td>
<td>1.22</td>
<td>0.53, 2.81</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7.4</td>
<td>8.3</td>
<td>0.99</td>
<td>0.44, 2.26</td>
</tr>
<tr>
<td>Chest pain/ischemia</td>
<td>7.4</td>
<td>8.3</td>
<td>0.93</td>
<td>0.39, 2.26</td>
</tr>
<tr>
<td>Coronary procedure/CABG</td>
<td>3.7</td>
<td>13.9</td>
<td>0.79</td>
<td>0.35, 1.79</td>
</tr>
<tr>
<td>Vascular events/cerebrovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>accidents</td>
<td>5.5</td>
<td>11.1</td>
<td>0.86</td>
<td>0.38, 1.95</td>
</tr>
<tr>
<td>All cardiovascular events</td>
<td>33.2</td>
<td>44.3</td>
<td>1.14</td>
<td>0.59, 2.20</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>5.5</td>
<td>0.78</td>
<td>0.32, 1.93</td>
</tr>
</tbody>
</table>

Testosterone and CV Risk in Men: A systemic review and meta-analysis of randomized placebo-controlled trials.


- Meta-analysis of randomized trials comparing commercially available testosterone with placebo.

- 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.”
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 age, 74 y) with serum TT 100-350 ng/dL or FT <50 pg/mL
- 209 Participants randomized to receive testosterone gel or placebo for 6 months
- Testosterone gel titrated 50 to 150 mg/d, based on serum testosterone level
- After dose adjustment, 16 men received 150 mg, 61 received 100 mg testosterone, and 29 received 50 mg
- Mean serum testosterone levels achieved were 574 (403) ng/dL in treatment group vs 292 (160) ng/dL in placebo group
- Both groups had high prevalence of hypertension, obesity, diabetes, hyperlipidemia, and CVD

TOM Trial: Results

- Primary endpoint: change from baseline in maximal voluntary muscle strength in leg-press exercise
- Secondary endpoints: chest-press strength, 50-m walking speed, and stair-climbing speed and power
- Compared with placebo group, testosterone-treated group had significantly greater improvements in leg-press and chest-press strength and in stair climbing while carrying a load
- In treatment arm, hematocrit and hemoglobin levels increased significantly, and HDL and LDL levels decreased
- Contrary to results of meta-analysis by Fernandez-Balsells et al, 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
### Table 3. Subjects with One or More Cardiovascular-Related Adverse Events.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Adverse Event</th>
<th>MedDRA-Classified Cardiac Event</th>
<th>Cardiovascular-Related Event no. of events</th>
<th>Atherosclerosis-Related Event</th>
<th>Method of Confirmation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Acute coronary syndrome and chest pain</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>Review of medical records</td>
</tr>
<tr>
<td>2</td>
<td>Chest pain</td>
<td></td>
<td>1</td>
<td>1</td>
<td>Examination by study physician</td>
</tr>
<tr>
<td>3</td>
<td>Syncope</td>
<td></td>
<td>1</td>
<td>Self-report</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Syncope</td>
<td></td>
<td>1</td>
<td>Self-report</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Myocardial infarction treated with angioplasty and placement of pacemaker</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Review of medical records</td>
</tr>
<tr>
<td>6</td>
<td>Myocardial infarction</td>
<td></td>
<td>1</td>
<td>1</td>
<td>Review of medical records</td>
</tr>
<tr>
<td>7</td>
<td>Angioplasty and coronary-artery bypass grafting</td>
<td></td>
<td>1</td>
<td>1</td>
<td>Review of medical records</td>
</tr>
<tr>
<td>8</td>
<td>Peripheral edema</td>
<td></td>
<td>1</td>
<td>Examination by study physician</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Peripheral edema</td>
<td></td>
<td>1</td>
<td>Examination by study physician</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Ectopy on ECG (premature ventricular contractions, couplets)</td>
<td>1</td>
<td>1</td>
<td>ECG evaluation by study physician</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Left ventricular strain pattern during exercise testing</td>
<td>1</td>
<td>1</td>
<td>ECG evaluation by study physician</td>
<td></td>
</tr>
</tbody>
</table>

### TOM Trial: Cardiovascular Adverse Events

#### Table 3. Subjects with One or More Cardiovascular-Related Adverse Events

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<th>Method of Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>ST-segment depression during exercise testing</td>
<td></td>
<td>1</td>
<td></td>
<td>ECG evaluation by study physician</td>
</tr>
<tr>
<td>13</td>
<td>Elevated blood pressure</td>
<td></td>
<td>1</td>
<td></td>
<td>Examination by study physician</td>
</tr>
<tr>
<td>14</td>
<td>Atrial fibrillation with rapid ventricular rate and shortness of breath and exacerbation of congestive heart failure, which necessitated hospitalization</td>
<td>2</td>
<td>2</td>
<td></td>
<td>Examination by study physician (atrial fibrillation) and report of primary care physician (exacerbation of congestive heart failure)</td>
</tr>
<tr>
<td>15</td>
<td>Stroke</td>
<td></td>
<td>1</td>
<td></td>
<td>Review of medical records</td>
</tr>
<tr>
<td>16</td>
<td>Elevated blood pressure and atrial fibrillation</td>
<td>1</td>
<td>1</td>
<td></td>
<td>Review of medical records</td>
</tr>
<tr>
<td>17</td>
<td>Peripheral edema</td>
<td></td>
<td>1</td>
<td></td>
<td>Examination by study physician</td>
</tr>
<tr>
<td>18</td>
<td>Peripheral edema</td>
<td></td>
<td>1</td>
<td></td>
<td>Examination by study physician</td>
</tr>
<tr>
<td>19</td>
<td>Elevated blood pressure</td>
<td></td>
<td>1</td>
<td></td>
<td>Examination by study physician</td>
</tr>
<tr>
<td>20</td>
<td>Tachycardia with fatigue</td>
<td></td>
<td>1</td>
<td></td>
<td>Self-report</td>
</tr>
<tr>
<td>21</td>
<td>Death, suspected myocardial infarction</td>
<td></td>
<td>1</td>
<td>1</td>
<td>Notification by physician</td>
</tr>
<tr>
<td>22‡</td>
<td>Peripheral edema</td>
<td></td>
<td>1</td>
<td></td>
<td>Examination by study physician</td>
</tr>
<tr>
<td>23</td>
<td>Congestive heart failure exacerbation</td>
<td></td>
<td>1</td>
<td></td>
<td>Review of medical records</td>
</tr>
</tbody>
</table>

TOM Trial: Cardiovascular Adverse Events

<table>
<thead>
<tr>
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<th>Cardiovascular-Related Event</th>
<th>Atherosclerosis-Related Event</th>
<th>Method of Confirmation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Syncope resulting in hospitalization</td>
<td></td>
<td>1</td>
<td></td>
<td>Self-report</td>
</tr>
<tr>
<td>2</td>
<td>Tachycardia</td>
<td></td>
<td>1</td>
<td></td>
<td>Examination by study physician</td>
</tr>
<tr>
<td>3</td>
<td>Elevated blood pressure</td>
<td></td>
<td>1</td>
<td></td>
<td>Examination by study physician</td>
</tr>
<tr>
<td>4</td>
<td>Arrhythmia–ectopy noted on ECG before exercise testing</td>
<td>1</td>
<td>1</td>
<td></td>
<td>Examination by study physician</td>
</tr>
<tr>
<td>5</td>
<td>Carotid bruit and carotid-artery plaque identified on ultrasoundography</td>
<td>1</td>
<td>1</td>
<td></td>
<td>Examination by study physician and review of medical records</td>
</tr>
</tbody>
</table>

AE, adverse event; CVD, cardiovascular disease; TOM, Testosterone in Older Men With Mobility Limitations.

TOM Trial: Cardiovascular Adverse Events

Caution is warranted in interpreting and extrapolating from these findings to other doses and formulations of testosterone or to other populations, particularly men with hypogonadism without CVD or mobility limitations

- Participants had high prevalence of chronic conditions, including preexisting heart disease, obesity, diabetes, and hypertension
- Cardiovascular AEs were not a planned primary or secondary outcome, and therefore, a structured analysis of cardiovascular AEs was not performed
- Clinical characteristics of the study population differ from those of most other populations in which testosterone therapy has been administered in a clinical setting or as part of a clinical trial
- Trials terminated early tend to overestimate treatment differences
- Trials that lack a consistent pattern in AEs and a small number of overall AEs suggest the possibility that the differences detected between the two groups may be due to chance

AE, adverse event; CVD, cardiovascular disease; TOM, Testosterone in Older Men With Mobility Limitations.
Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

- Purpose: to determine the association between testosterone therapy and all-cause mortality, MI and stroke in male veterans
- Retrospective national cohort study of men with low T levels (<300 ng/dL) who underwent coronary angio at a VA 2005-2011.
- 8709 men with low T; 1223 pts started on T therapy after a median of 531 days post angiography.
- At 3 yrs, Kaplan-Meier estimated cumulative % with events were 19.9% in the no-T group vs. 25.7% in the T group. No significant difference in the effect size of T therapy among those with and without CAD.

R. Vigen et al. JAMA 2013;310:1829-36
Death by Testosterone? We Think Not!

![Graph showing comparison between Untreated Group and T-Treated Group for Death, MI, Stroke, and All Events.]

Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men

- Cohort study of risk of acute non-fatal MI following an initial testosterone therapy (TT) prescription (n = 55,593). Evaluated the incidence rate of MI in 90 days following the initial prescription (post-prescription interval) with rate one year prior to prescription (pre-prescription interval) compared to PDE5 inhibitors.

- Results: post/pre-prescription rate ratio (RR) for TT prescription was 1.36; Men aged ≥ 65 RR was 2.19 for TT pts and 1.15 for PDE5 I, RR for TT prescriptions increased with age (0.95 for men < 55 yrs to 3.43 for pts ≥ 75 yrs). In men< 65 yrs, excess risk was confined to those with a prior history of heart disease,

- Conclusion: “In older men and in younger men with pre-existing diagnosed heart disease, the risk of MI following an initial TT prescription is substantially increased.”

WD Finkle, et al. PLOS ONE, Jan 2014, Vol 9, Issue 1 e85805
BUT - - - (based on the FDA statement)

- The diagnostic indications for testosterone therapy were not available.
- Results of lab testing of testosterone were not available. Levels not available.
- Testosterone exposure determined by a patient’s obtaining a prescription; unknown if pt actually filled the prescription, used it, got a refill, etc.
- 3-month follow up-? Adequate
- Fatal MI, CV mortality, stroke data not captured
- In testosterone cohort-higher comorbidity load
There are also studies in the literature showing just the opposite—
that testosterone reduces CV events and mortality:

Using a 5% national sample of Medicare pts, authors identified 6355 pts treated with at least one intramuscular injection of testosterone (T) between 1/1/1997 and 12/31/2005, and matched this cohort to 19,065 t non-users.

Results: T therapy was not associated with increased risk of MI (hr=0.85; 95% ci = 0.6-1.02). In men at high risk of MI, T therapy was associated with a reduced risk of MI (hr = 0.69; 95% ci = 0.53-0.92). No difference in risk for lower pts at lower risk.

Conclusions: older men treated with T did not have increased risk of MI. T was moderately protective against mi in men with high MI risk.
The TIMES 2 Study
Testosterone Replacement in Hypogonadal Men with Type 2 Diabetes and/or Metabolic Syndrome.

- This study tested the efficacy, safety, and tolerability of transdermal 2% testosterone gel over 12 mos. In 220 hypogonadal men with Type 2 diabetes and/or metabolic syndrome in men ≥ 40 years. Avg age = 60 years.
- Testosterone therapy reduced insulin resistance by 15.2% at 6 months (p=0.018) and 16.4% at 12 mos (p=0.006).
- Testosterone therapy improved glycemic control in Type 2 diabetes (Hbg AIC – 0.446%; p=0.035).

The TIMES 2 Study (cont’d)

- Testosterone (T) improved total cholesterol (4.77 control vs 4.49 T in mmol/L at 12 mos) and improved LDL cholesterol (2.75 C vs 2.59 T).
- Testosterone improved IIEF score, sexual desire scores, and intercourse satisfaction scores at 12 mos.
- Cardiovascular events occurred more commonly with placebo (10.7 vs 4.6%, p=0.095).
- **Conclusion**: Transdermal testosterone replacement therapy was associated with beneficial effects on insulin resistance, total, and LDL cholesterol, and sexual health in hypogonadal men with Type 2 diabetes and/or metabolic syndrome. Testosterone therapy was **not** associated with an increase CV events or other adverse events.

Effects of Testosterone Treatment in Older Men

Methods

- Assigned 790 men 65 years of age or older with a serum testosterone concentration of less than 275 ng/dL and symptoms suggesting hypoandrogenism to receive either testosterone gel or placebo gel for one year.

- Each man participated in one or more of three trials — the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial.

- Efficacy was assessed at baseline and at 3, 6, 9, and 12 months. Data on adverse events were collected during the treatment period and for 12 months afterward.

Efficacy

• Sexual function trial: The increase in testosterone levels in treated men was associated with significantly increased sexual activity, as well as significantly increased sexual desire and erectile function.

• Physical Function Trial: The percentage of men who had an increase of at least 50 m in the 6-minute walking distance did not differ significantly between the two study groups in the Physical Function Trial but did differ significantly when men in all three trials were included (20.5% of men who received testosterone vs. 12.6% of men who received placebo, P=0.003).

• Vitality trial: Testosterone had no significant benefit with respect to vitality, as assessed by the Functional Assessment of Chronic Illness Therapy–Fatigue scale

The rates of adverse events were similar in the two groups.

Exercise capacity in CHF Patients

- Caminiti 2009
- Malkin 2006
- Pugh 2004
- Iellamo 2010

Summary

Effect

Placebo Better Testosterone Better

Change in Exercise Time

Malkin CJ et al. Heart 2004;90:871-876
Summary

1. Erectile Dysfunction (ED) is related to CV risk factors
2. ED is common in patients with CAD
3. Low endogenous testosterone levels are associated with CV disease and atherosclerosis
4. There is controversy in the literature regarding the safety of Testosterone Replacement Therapy
5. There is a need for a prospective, controlled, blinded outcome study of T therapy with the primary endpoints being major adverse cardiovascular adverse events (MACE)
Thus the literature on whether exogenous testosterone is associated with CV events such as MI shows mixed results. There is a need for a large, prospective, randomized, placebo-controlled, double-blind, long-term study (~ 4-5 yrs), in which T or placebo is given to symptomatic hypogonadal men and the primary outcome is well defined cardiovascular events. These patients should have baseline T measurements, and T levels should be checked throughout the study.
Take home message:

Sexual dysfunction and hypogonadism are related to the cardiovascular system